In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

Filed: February 23, 2023

CRISTAL BELLO,	*	No. 13-349V
Petitioner,	*	Special Master Sanders
v.	*	
SECRETARY OF HEALTH AND HUMAN SERVICES,	*	Denial of Entitlement; Human Papillomavirus ("HPV" or "Gardasil") Vaccine; Premature Ovarian Failure/ Primary Ovarian Insufficiency ("POF/POI")
Respondent.	*	

Mark T. Sadaka, Law Offices of Sadaka Associates, LLC, Englewood, NJ, for Petitioner.
Kimberly Davey, U.S. Department of Justice, Washington, DC, for Respondent.

ENTITLEMENT DECISION[1]

On May 22, 2013, Cristal Bello ("Petitioner") filed a petition for compensation under the National Vaccine Injury Compensation Program[2] ("Vaccine Program" or "Program"). 42 U.S.C. § 300aa-10 to 34 (2012). Pet. at 1, ECF No. 1. The petition alleges that the human papillomavirus ("HPV" or "Gardasil") vaccination Petitioner received on June 4, 2010, caused her to suffer from premature ovarian failure ("POF").[3] *Id.* Petitioner's case was ultimately consolidated with a group of other cases all alleging that the HPV vaccine caused POF.

On August 30, 2021, I issued a Ruling on *Althen* prong one for this and seven other petitioners who had "consolidated their claims for the purpose of determining whether they have

[1] This Decision shall be posted on the United States Court of Federal Claims' website, in accordance with the E-Government Act of 2002, 44 U.S.C. § 3501 note (2012) (Federal Management and Promotion of Electronic Government Services). **This means the Decision will be available to anyone with access to the Internet**. In accordance with Vaccine Rule 18(b), a party has 14 days to identify and move to delete medical or other information that satisfies the criteria in § 300aa-12(d)(4)(B). Further, consistent with the rule requirement, a motion for redaction must include a proposed redacted decision. If, upon review, the I agree that the identified material fits within the requirements of that provision, such material will be deleted from public access.

[2] National Childhood Vaccine Injury Act of 1986, Pub L. No. 99-660, 100 Stat. 3755 ("the Vaccine Act" or "Act"). Hereinafter, for ease of citation, all "§" references to the Vaccine Act will be to the pertinent subparagraph of 42 U.S.C. § 300aa (2012).

[3] Premature ovarian failure, also known as primary ovarian insufficiency, is the "absence or irregularity of menses lasting at least four months, with menopausal levels of serum gonadotrophins in an adolescent girl or woman under 40 years of age. It may be temporary or permanent." *Dorland's Illustrated Medical Dictionary* 1, 945 (32nd ed. 2012) [hereinafter "*Dorland's*"]. I will refer to POF interchangeably with POI throughout this Decision.

presented a sufficient causation theory." *See* Findings of Fact and Conclusions of Law ("Findings of Fact") at 24, ECF No. 147; *Brayboy v. Sec'y of Health & Hum. Servs.,* No. 15-183V, 2021 WL 4453146 (Fed. Cl. Spec. Mstr. Aug. 30, 2021). I found that the theory presented, "while not applicable to all of them, does survive *Althen* prong one, [i]n instances where a petitioner can establish by a preponderant standard that she suffers from autoimmune POI." Findings of Fact at 24. Specifically, I found that the POI petitioners "have articulated a sound and reliable theory of how HPV vaccines could cause autoimmune POI via molecular mimicry." *Brayboy,* 2021 WL 4453146, at *1. In order to succeed under this theory and the remaining prongs of *Althen*, I explained that each POI petitioner must show it is more likely than not that she suffers from POI with an autoimmune etiology. *See id.* at *19. A determination of whether Petitioner suffers from autoimmune POI and factual analysis pursuant to *Althen* prongs two and three is now ripe for consideration.

After a careful review, Petitioner has failed to show by a preponderant standard that her POI is autoimmune in nature. As such, the record does not contain persuasive evidence that Petitioner's injury was caused-in-fact by her HPV vaccination via the biological mechanism she has proposed pursuant to *Althen* prong one. Accordingly, Petitioner's claim is hereby **DISMISSED.**

I. Procedural History

On May 22, 2013, Cristal Bello filed the first of the now-consolidated POI cases, alleging in her petition that the HPV vaccine she received on June 4, 2010, caused her to develop POI. Pet. at 1. She filed medical records, including an affidavit, on July 12, 2013, October 3, 2013, and December 13, 2013. Pet'r's Exs. 1–9, ECF Nos. 8, 15, 23. Petitioner filed a statement of completion on January 27, 2014. ECF No. 31.

On February 20, 2014, Respondent filed his Rule 4(c) report and denied that Petitioner was entitled to compensation. Resp't's Report at 7, ECF No. 35. Respondent argued that Petitioner had not satisfied her burden of proof under *Althen*, as "Petitioner ha[d] not submitted an expert report or any medical literature supporting the claim that the HPV vaccination caused her [POF]." *Id.* at 5–6 (citing *Althen v. Sec'y of Dep't of Health & Hum. Servs.,* 418 F.3d 1274, 1278–79 (Fed. Cir. 2005)). Additionally, "none of [P]etitioner's treating physicians attributed her problem to the HPV vaccine." *Id.* at 6. Respondent also generally contested numerous POI cases, including Petitioner's, and alleged that they were barred by the statute of limitations. *See* ECF No. 53 at 1. The presiding special master ordered Petitioner to file an expert report in support of her claim. *See* ECF Nos. 36–42. This matter was transferred to another special master on May 21, 2014. ECF Nos. 43–44.

Petitioner filed additional medical records on July 16 and November 18, 2014. Pet'r's Exs. 11–13, ECF Nos. 46, 52. On November 20, 2014, prior to the filing of Petitioner's expert report, the presiding special master held a status conference and identified POI cases in which a finding regarding onset would be relevant to the statute of limitations or causation. ECF No. 53; Min. Entry, docketed Nov. 20, 2014. At the conclusion of the status conference, "the parties agreed that in all pending POI cases . . . an expert hearing would be held to address the question of what constitutes the first symptom or manifestation of POI onset recognized as such by the medical profession at large." ECF No. 53 at 1; *see also Culligan v. Sec'y of Health & Hum. Servs.*, No. 14-

318V, 2016 WL 3101981, at *3 (Fed. Cl. Spec. Mstr. June 2, 2016) (internal citations omitted). The presiding special master identified Petitioner's case as one that did not have a statute of limitations issue, but that a finding regarding onset would be relevant to establishing causation. ECF No. 53 at 1. The special master therefore established that the *Culligan* case would serve as the test case, with all others trailing, including Petitioner's. *See id.* The special master indicated that 1) "a timeliness determination would then be made based on the evidence presented at the *Culligan* hearing;" 2) all petitioners would consent to share their medical records; and 3) "similar hearings would not be conducted in other POI cases[.]" *Culligan,* 2016 WL 3101981, at *3–*4. In advance of the onset hearing, the presiding special master ordered the POI petitioners to file an expert report addressing several questions, including "what constitutes 'the first symptom or manifestation of [POI/POF] onset[.]'" ECF No. 53 (citing *Cloer v. Sec'y of Health & Hum. Servs.*, 654 F.3d 1322, 1340 (Fed. Cir. 2011)).

Prior to the *Culligan* hearing, Petitioner filed a status report on December 17, 2014, consenting to the disclosure of her case information to other POI/POF petitioners. ECF No. 54. Petitioner filed medical records containing laboratory test results on February 18, 2015. Pet'r's Ex. 14, ECF No. 58. On March 3, 2015, Petitioner filed expert reports from Drs. Yehuda Shoenfeld and Orit Pinhas-Hamiel, along with supporting medical literature on a compact disc on April 15, 2015. *See* Pet'r's Exs. 15–18, 19 Tabs A1–A19, Tabs 1–95, 20 Tabs 1–14, ECF Nos. 59–62. A consolidated hearing regarding the issue of onset of POI was held on June 16–17, 2015, after which the presiding special master reiterated that Petitioner's case could proceed consistent with the findings in *Culligan*. *See* Min. Entry, docketed June 18, 2015; *see also* No. 14-318V, ECF No. 79; *Culligan*, 2016 WL 3101981, at *5. *Culligan* was ultimately dismissed after the special master determined the case was time-barred. *See Culligan*, 2016 WL 3101981, at *11.

On August 11, 2016, the presiding special master held a status conference with the parties and stated that while Petitioner's case was not barred by the statute of limitations, Petitioner would need to undergo additional genetic and autoimmune testing in support of her claim. ECF No. 73 at 1. Petitioner's counsel indicated that he would likely retain the same causation expert for all of the remaining POI cases, and Respondent indicated that his stance on further consolidation would depend on whether the POI petitioners presented the same theory of causation. *See, e.g.*, ECF No. 73; *see also* No. 15-183V, ECF No. 15 at 1. On September 8, 2016, Petitioner filed a status report indicating "consent[] to the disclosure of her case information to other POI petitioners, including the POI petitioners whose petitions were filed after [*Culligan*]." ECF No. 73 at 2; ECF No. 76. Petitioner filed several status reports regarding the identity and progress of the POI petitioners' experts. ECF Nos. 77–78. Petitioner submitted medical records on January 5, 2017. Pet'r's Exs. 21–23, ECF No. 80.

This case was reassigned to me on January 9, 2017. ECF Nos. 82–83. Petitioner filed additional medical records and a supplemental statement of completion on March 23, 2017. Pet'r's Exs. 24–25, ECF Nos. 90–92. Following several extensions of time, on May 22, 2017, I *sua sponte* suspended Petitioner's deadline for the filing of an expert report, in light of circumstances concerning her counsel. ECF No. 94. On June 14, 2017, Petitioner's counsel filed a motion to substitute a new attorney in Petitioner's case, which I granted the same day. ECF Nos. 95–96. The next day, I reinstated Petitioner's deadline for the filing of her expert report. ECF No. 97; Non-PDF Order, docketed June 15, 2017.

On August 1, 2017, Petitioner submitted expert reports from Drs. Orit Pinhas-Hamiel, Felice Gersh, and Yehuda Shoenfeld. Pet'r's Exs. 27–90, ECF Nos. 98, 100–06, 108. The expert report from Dr. Shoenfeld, Pet'r's Ex. 31, was filed in each of the POI petitioners' cases and did not discuss case-specific information. *See, e.g.*, No. 15-183V, ECF No. 40. The reports from Drs. Pinhas-Hamiel and Gersh contained case-specific information. *See* Pet'r's Exs. 27, 29, ECF No. 98. Following the submission of Petitioner's expert reports, I held a status conference with the parties on August 15, 2017. ECF No. 99; Min. Entry, docketed Aug. 15, 2017. After some discussion, the parties agreed that Respondent should proceed with filing responsive expert reports addressing the first prong of *Althen*, as Petitioner's theory was the same in each of the POI petitioners' cases. *See* ECF No. 99. The parties agreed that consolidation remained appropriate. *See* No. 15-183V, ECF No. 41.

Following several extensions of time, Respondent filed responsive expert reports on *Althen* prong one from Drs. Thomas Forsthuber, David Frankfurter, and Robert Yokel, along with supporting medical literature on May 14, 2018. Resp't's Exs. A, A.1–A.31, B–D, D Tabs 1–47, E, E Tabs 1–47, ECF Nos. 110–20. Petitioner filed supplemental expert reports on prong one from Drs. Pinhas-Hamiel and Shoenfeld on September 11, 2018. Pet'r's Exs. 91–92, ECF No. 122. She filed medical literature on October 17, 2018. Pet'r's Ex. 93, ECF No. 123. On November 12, 2018, Petitioner filed a consented motion to substitute a new attorney, which was granted. ECF No. 124. Respondent submitted supplemental expert reports from Drs. Forsthuber, Frankfurter, and Yokel on November 19, 2018. *See* Resp't's Exs. D Tabs 2–3, G, G Tabs 1–3, H, H Tabs 1–23, I, I Tabs 1–2, ECF Nos. 125, 127.

On December 6, 2018, Petitioner filed another consented motion to substitute counsel and requested for one attorney to handle all the POI petitioners' cases. ECF No. 126. I held a status conference with the parties on December 18, 2018, regarding Petitioner's motion and whether counsel was prepared to handle the workload associated with these cases. ECF No. 128; Min. Entry, docketed Dec. 18, 2018. Following the conference and counsel's representations, Mr. Mark Sadaka took over Petitioner's claim on December 18, 2018. *See* ECF No. 128.

I held a status conference with the parties on March 21, 2019, to discuss the parties' arguments with respect to *Althen* prong one. *See* ECF Nos. 129–30, 132; Min. Entry, docketed Mar. 21, 2019. The same day, Respondent filed medical literature. Resp't's Ex. J, ECF No. 131. On May 6, 2019, Petitioner filed an additional supplemental expert report from Dr. Shoenfeld, with supporting medical literature. Pet'r's Exs. 94–116, ECF Nos. 133–35. Respondent submitted supplemental reports from Drs. Forsthuber and Frankfurter, along with medical literature on September 27–30, 2019. Resp't's Exs. K, K Tabs 1–9, L, L Tabs 1–19, ECF Nos. 138–40. On October 1, 2019, Petitioner filed medical literature. Pet'r's Exs. 117–18, ECF No. 141.

The parties appeared for a status conference on December 6, 2019, during which I informed the parties that the best way to proceed would be for the parties to submit briefs on *Althen* prong one. *See* Min. Entry, docketed Dec. 6, 2019; *see also* No. 15-183V, ECF No. 80. The *Brayboy* case, No. 15-183V, was ultimately named as the lead case. ECF No. 80. The POI petitioners requested "the opportunity to use facts from [*Brayboy*] . . . to provide factual context to the parties' arguments[]" related to prong one in their briefs. *See id.* I agreed and after numerous extensions of time, Petitioner accordingly filed a HIPAA waiver on May 1, 2020. *See* ECF Nos. 142–45. The

parties then filed their briefs on *Althen* prong one in the lead case on June 18, September 22, and November 20, 2020, respectively. *See* No. 15-183V, ECF Nos. 86, 88, 90.[4]

Following the submission of the parties' briefs on *Althen* prong one, I issued a ruling on prong one only on August 30, 2021. ECF No. 147; *Brayboy,* 2021 WL 4453146, at *1. On December 14, 2021, consistent with my ruling, I held a status conference in this matter to discuss whether preponderant evidence has been submitted showing that Petitioner suffers from POI with an autoimmune etiology so that she may proceed under *Althen* prongs two and three. Sched. Order at 1, ECF No. 149. The parties agreed updated medical records would be needed and I awarded Petitioner sixty days to file such records. *See id.*

On February 14, 2022, Petitioner filed an unopposed motion for an extension of time to file the requested information. ECF No. 150. I stayed Petitioner's motion and ordered her to file 1) a status report indicating whether the case will proceed with expert reports on *Althen* prongs two and three or be dismissed; and/or 2) an explicit motion to supplement Petitioner's request for sixty days to file medical records containing additional objective testing, including a timeline for the collection and submission of such filings. ECF No. 151. On March 15, 2022, Petitioner filed a supplemental motion for an extension of time alleging that she planned to undergo further antibody testing and providing a timeline. ECF No. 152. Respondent noted that he did not see the particular relevance to such testing when the last medical record in this matter was from 2017 and the onset of Petitioner's symptoms was approximately twelve years ago. *Id.* at 2.

In response to Petitioner's status report, I held a status conference with the parties on April 12, 2022. Min. Entry, docketed Apr. 12, 2022. During the conference, the parties discussed the relevance of additional antibody testing, along with the additional factors set forth in my ruling on *Althen* prong one that will aid in my determination of vaccine causation. *See* ECF No. 153; *see also* Findings of Fact, ECF No. 147. I noted such test results are particularly unhelpful following prior negative results that were recorded closer in time to Petitioner's initial symptom manifestation and diagnosis. ECF No. 153. Petitioner requested sixty days to file a status report or other filing identifying evidence regarding her basis to proceed, aside from any recent positive antibody results, and I granted her request. *See id.*

Following one extension of time, on June 14, 2022, Petitioner filed updated antibody test results from April 8, 2022, along with an affidavit indicating she was still in the process of arranging to undergo ovarian antibody testing. Pet'r's Exs. 121–22, ECF Nos. 156–57. Petitioner also filed a status report that cited to her positive antinuclear antibody ("ANA")[5] tests on July 27, 2011, and February 6, 2017, recurrent rashes "that could be psoriasis," and her treater's note that says her POF "likely [has an] autoimmune etiology[,]" to support her claim. ECF No. 158 (citing Pet'r's Ex. 5 at 6; Pet'r's Ex. 2 at 41; Pet'r's Ex. 9 at 76). Petitioner requested "additional time" to

[4] As the *Brayboy* case was selected to be the lead case for the POI petitioners, the briefs in support of *Althen* prong one were filed in that case only but on behalf of all POI petitioners, including Petitioner.

[5] Antinuclear antibodies are "antibodies directed against nuclear antigens; ones against a variety of different antigens are almost invariably found in systemic lupus erythematosus and are frequently found in rheumatoid arthritis, scleroderma (systemic sclerosis), Sjögren syndrome, and mixed connective tissue disease. Antinuclear antibodies may be detected by immunofluorescent staining. Serologic tests are also used to determine antibody titers against specific antigens." *Dorland's* at 101.

obtain antibody testing for anti-ovarian and/or anti-adrenal autoantibodies. *See id.* at 2. Petitioner maintained that her positive ANA tests, along with her clinical presentation are enough to allow her claim to continue pursuant to *Althen* prongs two and three. *Id.*

On June 23, 2022, I denied Petitioner's request for additional time to undergo further antibody testing. ECF No. 159 at 2. I cautioned Petitioner that "recent antibody tests are generally unhelpful in establishing POI etiology, particularly when there is a prior negative antibody test history. Without more, Petitioner will likely be unsuccessful in establishing the applicability of the [] biological mechanism." *See id.* I ordered Petitioner to file an expert report on *Althen* prongs two and three, addressing the factors enumerated in my ruling on *Althen* prong one, aside from any recent positive antibody results if there have been years between such results and the onset of Petitioner's symptoms, and/or prior negative results. *Id.*; *see also* ECF No. 162.

Petitioner filed updated medical records on August 22, 2022. Pet'r's Ex. 123, ECF No. 163. She also filed expert reports on *Althen* prongs two and three from Drs. David Axelrod and Orit Pinhas-Hamiel, along with supporting medical literature, on September 21, 2022. Pet'r's Exs. 124–37, ECF Nos. 164–66. Petitioner submitted the literature cited in such reports on November 23, 2022. Pet'r's Exs. 138–46, ECF No. 171. Following one extension, Respondent submitted responsive expert reports from Drs. Thomas Forsthuber and Corrine Welt, along with supporting medical literature on November 28, 2022. Resp't's Exs. M, M-1–M-9, N, N-1–N-19, O, ECF Nos. 167, 169, 172–73. With consideration of the factors enumerated in my ruling on *Althen* prong one, a determination of Petitioner's vaccine causation pursuant to *Althen* prongs two and three is now ripe for consideration.

II. Medical History

Petitioner's medical history is relevant for migraine headaches, depression and anxiety, bipolar disorder, asthma, sleep disorder, and two elective pregnancy terminations at ages 20 and 22. *See* Pet'r's Ex. 4 at 3–4, ECF No. 8-5; Pet'r's Ex. 5 at 6, ECF No. 8-6. Specifically, on September 19, 2006, Petitioner had a positive pregnancy test. Pet'r's Ex. 8 at 7, 43, ECF No. 15-2. She reported that her last two menstrual cycles began "on or about [July 19, 2006,]" and August 26, 2006, respectively. *Id.* at 43. Petitioner subsequently underwent a pregnancy termination on October 13, 2006. *See id.* at 8, 41. The same day, she reported that her last menstrual period was on August 28, 2006. *Id.* at 37. Petitioner noted Depo Provera injections[6] as her current birth control method. *Id.* at 41. Petitioner's Depo Provera injection record shows that she received only one dose of Depo Provera on October 13, 2006. *Id.* at 48.

During a visit on April 26, 2007, Petitioner noted that her "last normal menstrual period" occurred during August of 2006, and she was "not sure" about the start dates of previous cycles.

[6] Depo Provera is the trademark preparation of medroxyprogesterone acetate. *Dorland's* at 492. Medroxyprogesterone acetate is used as an intramuscular, long-acting contraceptive. *Id.* at 1120. It is also a "progestin administered orally for treatment of secondary amenorrhea and dysfunctional uterine bleeding, induction of menses, prevention and treatment of endometrial hyperplasia in postmenopausal hormone replacement therapy, and testing for endogenous estrogen production; administered orally or intramuscularly as an antineoplastic in treatment of metastatic endometrial, breast, and renal carcinoma[.]" *Id.*

Id. at 43. Petitioner had a pregnancy test, which was negative, and her treater wrote that Petitioner "w[ould] return in [two] weeks if no menses [wa]s reported." *See id.* Petitioner indicated that Depo Provera was her most recent form of birth control. *Id.* Five months later, on September 26, 2007, Petitioner returned and reported that her last normal menstrual period was on August 27, 2007, and again reported Depo Provera as her last method of birth control. *Id.* at 45. The record does not note that Petitioner's cycle resumed at any point between August 2006 and August of 2007. *See generally id.* at 1–47. Later that year, on November 28, 2007, Petitioner was prescribed Ortho Tri-cyclen[7] and her last menstrual period was noted as November 27, 2007. *Id.* at 20. The record does not note if Petitioner menstruated during the month of October in 2007. *See id.*

Petitioner's second positive pregnancy test occurred on May 7, 2008, following an ultrasound. *Id.* at 37. She noted that her last menstrual period was on March 10, 2008. *Id.* The records show this pregnancy was terminated but the exact date of this procedure is unclear.[8] *Id.* at 13, 24–31, 33, 39. Petitioner's medical records reflect she requested a prescription for hormonal contraception on March 20, 2009. *Id.* at 31. Petitioner was again prescribed oral contraceptives on May 25, 2010. Pet'r's Ex. 2 at 61, ECF No. 8-3. Office notes on this date indicate that her last menstrual period was on May 23, 2010. *Id.* at 66. At age 23, Petitioner received the HPV vaccine in question on June 4, 2010. *Id.* at 64.

On August 6, 2010, Petitioner presented to her gynecologist, Lana Selitsky, M.D., reporting complaints of hot flashes for the past two weeks. *Id.* at 59. She also complained of a three-pound weight loss, a "change in her energy status[,]" and vaginal dryness. *Id*. Dr. Selitsky ordered lab work, which showed post-menopausal levels of follicle stimulating hormone ("FSH")[9] (78.2, with

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[7] Ortho Tri-cyclen is the trademark preparation for therapeutic regimens of norgestimate and ethinyl estradiol. *Dorland's* at 1339. Norgestimate is a synthetic progestational agent having little androgenic activity; used in combination with an estrogen component as an oral contraceptive. *Id.* at 1290. Ethinyl estradiol is "one of the most potent estrogens. It is used in combination with a progestational agent in oral contraceptives and contraceptive patches, and administered orally in hormone replacement therapy[.]" *Id.* at 651.

[8] Petitioner's record reflects that she underwent an ultrasound on May 7, 2008, revealing a pregnancy. Pet'r's Ex. 8 at 37. On that date, she noted that her last menstrual period occurred on March 10, 2008. *Id.* Her records include an "abortion anesthesia record" dated March 20, 2009. *See id.* at 33. This record does not appear to relate to her May 7, 2008 pregnancy. Indeed, her records do not include documentation of a pregnancy termination in 2008. However, I must note that several of Petitioner's records during this time period are undated, handwritten, and unclear. For example, the "preoperative exam" record containing a reference to Petitioner's last menstrual period on March 10, 2008, (consistent with her May 7, 2008 ultrasound report), is undated or the date appears to have been inadvertently covered. *See id.* at 39. It also contains a notation that Petitioner's pregnancy was 9–10 weeks along. *Id.* The evidence therefore shows Petitioner's second pregnancy was likely terminated on May 7, 2008, but without additional context, I will not make such a determination by a preponderant standard.

[9] The follicular stimulating hormone ("FSH") is "an anterior pituitary [] hormone that is a gonadotropic hormone[] . . . that stimulates the growth and maturation of ovarian follicles, stimulates estrogen secretion, [and] promotes the endometrial changes characteristic of the first portion (proliferative phase) of the mammalian menstrual cycle . . . ." *Dorland's* at 870.

post-menopausal range of 23–336)[10] and luteinizing hormone ("LH")[11] (53.2, with post-menopausal range of 15–54).[12] *Id.* at 50. Petitioner's labs also showed low monocytes and a normal thyroid stimulating hormone ("TSH"). *Id.* at 50, 53. Petitioner underwent repeat labs on August 18, 2010, which showed a post-menopausal FSH level of 52.3. Pet'r's Ex. 3 at 25, ECF No. 8-4. Approximately one month later, on September 22, 2010, Petitioner's labs yielded normal FSH/LH levels of 14.4 and 14.2, respectively. Pet'r's Ex. 2 at 48.

On December 7, 2010, Petitioner faxed a note to gynecologist and reproductive endocrinologist Dov Goldstein, M.D. Pet'r's Ex. 3 at 32. Petitioner reported that she began having hot flashes "[i]n the beginning of August [of 2010]," and "mentioned it to [her gynecologist,]" Dr. Selitsky. *Id.*; *see also* Pet'r's Ex. 2 at 59 (wherein on August 6, 2010, Petitioner complained to Dr. Selitsky of hot flashes for the past two weeks). Petitioner continued that her gynecologist then ran tests, showing that Petitioner's FSH levels had been "abnormally high." Pet'r's Ex. 3 at 32. Petitioner wrote to Dr. Goldstein that during said time in August of 2010, she had "missed [her] menstrual cycle for about [three] months[,]" so her gynecologist took her off birth control and continued to monitor her hormone levels for the next two months. *Id.* Petitioner indicated that her hot flashes then dissipated but they were now "back and worse than before." *Id.* She complained of weight loss but that her appetite was increasing. *Id.* Petitioner also noted that her period was "again" two weeks late. *Id.* at 32–33. Among Dr. Goldstein's visit notes is a handwritten examination note regarding Petitioner that is undated, unsigned, and without context.[13] *See id.* at 7. It appears to reflect that Dr. Goldstein's impression was once listed as "[rule out] premature ovarian failure." *Id.* Dr. Goldstein started Petitioner on hormone replacement therapy with a Vivelle-Dot patch[14] (estrogen) and Provera[15] (a synthetic progestin) per this note, but the chronology is unknown.[16] *Id.*

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[10] A normal FSH level for a woman still menstruating is 4.7 to 21.5 IU/L, although normal value ranges may vary slightly among different laboratories. *See Follicle-stimulating hormone (FSH) blood test,* MOUNT SINAI, https://www.mountsinai.org/health-library/tests/follicle-stimulating-hormone-fsh-blood-test (last visited Jan. 31, 2023).

[11] The luteinizing hormone ("LH") is an "anterior pituitary hormone that . . . acts with follicle-stimulating hormone to promote ovulation as well as secretion of androgens and progesterone. It instigates and maintains the second (secretory) portion of the mammalian estrus and menstrual cycle." *Dorland's* at 870.

[12] A normal LH level for a woman prior to menopause is 5 to 25 IU/L, although normal value ranges may vary slightly among different laboratories. *See Luteinizing hormone (LH) blood test,* MOUNT SINAI, https://www.mountsinai.org/health-library/tests/luteinizing-hormone-lh-blood-test (last visited Jan. 31, 2023).

[13] It is extremely difficult to decipher. *See* Pet'r's Ex. 3 at 7.

[14] The Vivelle-Dot patch is the trademark preparation for estradiol. *Dorland's* at 2069. Estradiol is "1. the most potent naturally occurring ovarian and placental estrogen in mammals; it prepares the uterus for implantation of the fertilized oocyte and promotes the maturation and maintenance of the female accessory reproductive organs and secondary sex characters . . . 2. a preparation of this hormone used in estrogen replacement therapy[.]" *Id.* at 649.

[15] *See supra,* note 6 (defining Depo Provera).

[16] As this note is undated, the exact start date of Petitioner's use of hormone replacement therapy is not clear. Her later records reflect that as of March 11, 2011, she had begun taking Provera. Pet'r's Ex. 3 at 5. Her March 24, 2011 medical record seems to reflect that she stopped using the Vivelle-Dot patch because it was not helping her hot flashes. *Id.* By October 4, 2011, Dr. Goldstein wrote that Petitioner had "stopped" Vivelle and she was ordered to re-start the Vivelle-Dot patch and Provera. *See id.* at 2. On March 17, 2012,

Petitioner underwent repeat testing on December 16, 2010, revealing an elevated FSH and LH, and a negative ANA. *See* Pet'r's Ex. 2 at 41–42. Her testing also revealed a normal rheumatoid factor[17] and erythrocyte sedimentation rate ("ESR").[18] *Id.* Petitioner underwent a pelvic ultrasound on December 17, 2010, that showed a normal-sized right ovary with a follicle measuring 12 x 9 mm, but the left ovary was not clearly seen. Pet'r's Ex. 3 at 13. A repeat pelvic ultrasound was performed on February 7, 2011, and was normal with one follicle on her right ovary measuring 5 x 4 mm, except the left ovary was again not clearly seen. *Id.* at 10–11. During this procedure, Dr. Goldstein noted that Petitioner's last menstrual cycle was in November of 2010. *Id.* at 10.

By March 1, 2011, Dr. Goldstein noted that Petitioner was still having "lots of" hot flashes. *Id.* at 5.[19] On March 11, 2011, Dr. Goldstein recorded that Petitioner had "no hot flashes for [four to five] days]" and that she "[t]ook Provera." *Id.* On March 24, 2011, Dr. Goldstein noted that Petitioner "stop[ped] the Vivelle[-Dot patch] but was still getting hot flashes[.]"[20] *Id.*

On July 27, 2011, Petitioner underwent additional lab testing that showed a positive ANA at 1:160. Pet'r's Ex. 9 at 72, ECF No. 23-2. During this visit, Petitioner recounted her medical history of anxiety, asthma, depression, and type-2 diabetes mellitus.[21] *Id.* at 7. Petitioner returned to Dr. Goldstein on October 4, 2011. Pet'r's Ex. 3 at 2. He noted that Petitioner continued to experience fluctuating FSH levels and had discontinued her use of the Vivelle-Dot, due to a recurrence of her hot flashes. *Id.* Based on Petitioner's history, Dr. Goldstein diagnosed her with amenorrhea[22] and POF with hot flashes. *Id.* Dr. Goldstein ordered Petitioner to restart the Vivelle-Dot and Provera.[23] *Id.*

Dr. Gleicher noted that Petitioner had been taking hormone replacement therapy but she had stopped it one month prior to that appointment. Pet'r's Ex. 5 at 6. It therefore appears that Petitioner was on hormone replacement therapy off and on from approximately March of 2011 through February of 2012.

[17] Rheumatoid factor refers to "antibodies directed against antigenic determinants, i.e., Gm, in the Fc region of the IgG class of immunoglobulins; these are found in the serum of about 80 percent of persons with classical or definite rheumatoid arthritis but only about 20 percent of those with juvenile rheumatoid arthritis . . . Rheumatoid factors also occur in other connective tissue diseases and some infectious diseases." *Dorland's* at 676.

[18] The erythrocyte sedimentation rate refers to "the rate at which erythrocytes precipitate out from a well-mixed specimen of venous blood . . . an increase in rate is usually due to elevated levels of plasma proteins, especially fibrinogen and immunoglobulins, which decrease the zeta potential on erythrocytes by dielectric shielding and thus promote rouleau formation. It is increased in monoclonal gammopathy, hypergammaglobulinemia due to inflammatory disease, hyperfibrinogenemia, active inflammatory disease, and anemia[.]" *Dorland's* at 1594. An erythrocyte is a red blood cell. *Id.* at 644.

[19] Such notations by Dr. Goldstein are likewise handwritten and extremely difficult to decipher.

[20] This notation is handwritten and difficult to decipher.

[21] Other than this self-reported diagnosis of type-2 diabetes mellitus, there is no other mention or diagnosis, of diabetes in Petitioner's medical records. Petitioner's own expert Dr. Axelrod highlighted this point. *See* Pet'r's Ex. 124 at 2. Type-2 diabetes mellitus is "one of the two major types of diabetes mellitus, characterized by peak age of onset between 50 and 60 years, gradual onset with few symptoms of metabolic disturbance . . . and no need for exogenous insulin; dietary control with or without oral hypoglycemic is usually effective. Obesity and genetic factors may also be present. Diagnosis is based on laboratory tests indicating glucose intolerance." *Dorland's* at 506.

[22] Amenorrhea is the absences of abnormal stoppage of the menses. *Dorland's* at 59.

[23] These notations are also handwritten and mostly illegible.

On March 17, 2012, Petitioner presented to gynecologist Norbert Gleicher, M.D. Pet'r's Ex. 5 at 6. Dr. Gleicher wrote that Petitioner began menstruating at age 15, but that her periods had since ceased. *Id.* Petitioner reported that her last period was in October of 2010. *Id.* Dr. Gleicher noted that Petitioner had a positive ANA during "[July of 2011]" and that she was diagnosed with POF by Dr. Goldstein in 2010. *Id.* He also noted that Petitioner was on "[hormone replacement therapy], which she stopped [one] month ago[.]" *Id.* Dr. Gleicher wrote that Petitioner was "still allegedly producing mature follicles on [her ultrasound.]" *Id.* at 7. Dr. Gleicher's impression was that her POF was "likely autoimmune[.]" *Id.* He ordered additional lab tests on March 17, 2012, which showed a negative ANA. *Id.* at 29. Such lab results were negative or normal for autoimmune serologies, including lupus anticoagulant,[24] immunoglobulins,[25] anti-cardiolipin antibody,[26] beta-2 glycoprotein, thyroid antibodies, liver function testing, testosterone, dehydroepiandrosterone,[27] anti-Müllerian hormone,[28] anti-adrenal antibodies, anti-ovarian antibodies, thyrotropin receptor antibodies,[29] and prolactin.[30] *Id.* at 23–29, 33–36, 47. Her genetic testing for Fragile X mutation[31] was also negative. *Id.* at 31, 34.

Petitioner presented to another gynecologist on April 23, 2012, who noted her recent negative autoimmune workup. *See id.* at 4. Petitioner's treater noted her family history of scleroderma[32] and diabetes-mellitus. Pet'r's Ex. 6 at 3–5, ECF No. 8-7; Pet'r's Ex. 23 at 115, ECF No. 80-3. Petitioner underwent DNA testing on August 9, 2012, which was mostly normal. Pet'r's Ex. 12 at 11, ECF No. 52-2. However, Petitioner's anti-Müllerian hormone was abnormal at < 0.16 ng/mL (normal range for 25-year-old is 0.65–16.40 ng/mL). Pet'r's Ex. 5 at 13.

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[24] Lupus anticoagulant is "a circulating anticoagulant that inhibits the conversion of prothrombin to thrombin, found in 5 to 10 per cent of patients with systemic lupus erythematosus, but also seen in other disorders." *Dorland's* at 102.

[25] An immunoglobulin is an antibody used by the immune system to identify and neutralize foreign objects such as bacteria and viruses (antigens). *Dorland's* at 919.

[26] Anti-cardiolipin antibody is "an antibody directed against cardiolipin, seen with increased frequency in systemic lupus erythematosus; its presence correlates with increased risk for thrombotic events." *Dorland's* at 100.

[27] Thyroid autoantibodies refer to those "against thyroid peroxidase, thyroglobulin, and thyroid-stimulating hormone receptors, seen in autoimmune thyroiditis." *Dorland's* at 180.

[28] The anti-Müllerian hormone plays a role in the development of a fetus's sex organs (primarily the uterine tubes and uterus in females and appendix testis and prostate in males) while in-utero. *Dorland's* at 870.

[29] Thyrotropin receptor antibodies are autoantibodies against "a glycoprotein anterior pituitary hormone (28,000 daltons) that promotes the growth of, sustains, and stimulates hormonal secretion of the thyroid gland. Called also *thyroid-stimulating hormone." Dorland's* at 1926.

[30] Prolactin is an anterior pituitary hormone that stimulates the formation of milk in mammals and "has many other effects, including [providing] essential roles in the maintenance of immune system functions." *Dorland's* at 1524.

[31] A Fragile X mutation is indicative of Fragile X syndrome. It is defined as "an X-linked syndrome associated with a fragile site at locus Xq27.3, characterized by intellectual disability, enlarged testes, high forehead, and enlarged jaw and ears in most males and mild intellectual disability in many heterozygous females." *Dorland's* at 1830.

[32] Scleroderma is an autoimmune condition that involves the "chronic hardening and thickening of the skin[,]" and has two forms, localized and systemic scleroderma. *Dorland's* at 1679.

On March 28, 2013, Petitioner presented to rheumatologist Soumya Reddy, M.D., for evaluation of her POF and a reported positive ANA "in 2011[.]"[33] Pet'r's Ex. 6 at 1. Petitioner reported she was experiencing hot flashes. *Id.* She also reported that she had developed a rash inside her ears in "mid 2012" that an ENT specialist thought was "maybe eczema[34] or psoriasis[,]"[35] and it improved with steroid cream. *Id.* Dr. Reddy wrote that Petitioner did not seek treatment with dermatology. *Id.* Petitioner stated she "gets [an] intermittent 'bumpy rash' [on her] back, stomach, and arm . . . [w]ith scaly/dry area[s]/redness[, m]ost severe [on her] scalp." *Id.* Dr. Reddy recorded that Petitioner's grandmother has scleroderma and that her sister has a "similar scalp rash/lesions." *Id.* Upon exam, Dr. Reddy indicated that Petitioner had joint pain in her hands, hips, and knees (that was worse during winter), but no joint swelling. *Id.* Dr. Reddy also noted Petitioner had "mild flakiness at [her] hairline[] and inside [her left] ear," but wrote there was "no obvious rash or psoriasis." *Id.* at 3. Dr. Reddy did not find any evidence of an autoimmune rheumatologic disease in Petitioner, and assessed her with POF, positive ANA, and a rash. *Id.* In light of Petitioner's family history of scleroderma and Petitioner's reported positive ANA, Dr. Reddy ordered additional testing. *Id.* at 3–5. No labs from March of 2013 appear to be contained in the medical records. *See* Pet'r's Ex. 24 at 4, ECF No. 90-1.

Petitioner continued to receive treatment for her POF throughout 2013–2016. Petitioner underwent laboratory testing for adrenal autoantibodies on February 5, 2015, which was negative. Pet'r's Ex. 14 at 1, ECF No. 58-2. On February 6, 2017, at the direction of Dr. Reddy, Petitioner underwent repeat testing that showed a positive ANA at a dilution of >1:80. Pet'r's Ex. 24 at 38. Petitioner's antibody testing, including for SCL-70 antibodies (used to test for scleroderma), was negative. *Id.* at 7–10. Testing for inflammatory markers, including ESR and c-reactive protein ("CRP"),[36] was normal. *Id.* at 41. During a follow-up with Dr. Reddy on March 20, 2017, Dr. Reddy noted Petitioner's positive ANA, POF, rash, unintentional weight change, and chronic fatigue under diagnoses. *Id.* at 1.

On September 21, 2021, Petitioner presented to dermatologist Marisa Garshick, M.D., complaining of "multiple spots on the skin." Pet'r's Ex. 123 at 10, ECF No. 163-1. Dr. Garshick assessed Petitioner with acne and dermatofibroma,[37] among other conditions acquired through chronic sun exposure, but did not diagnose her with psoriasis. *Id.* at 12–13.

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[33] The date of this positive ANA was July 27, 2011. Pet'r's Ex. 9 at 72.

[34] Eczema is "any of various pruritic, papulovesicular types of dermatitis occurring as reactions to endogenous or exogenous agents. In acute types there may be erythema, edema, inflammatory infiltrates in the dermis, vesiculation, crusting, and scaling. In chronic types there may be lichenification, skin thickening, signs of excoriation; and areas of hyperpigmentation or hypopigmentation." *Dorland's* at 592.

[35] Psoriasis refers to "any of a group of common chronic, squamous dermatoses with variable symptoms and courses; some are inherited. Principal histologic findings are [] microabscesses and [] pustules; also seen are rounded, circumscribed, erythematous, dry, scaling patches of various sizes, covered by gray, silvery, or white, umbilicated, lamellar scales. The most common sites are extensor surfaces, nails, scalp, genitalia, and the lumbosacral region." *Dorland's* at 1547.

[36] C-reactive protein refers to a protein made by the liver. *Dorland's* at 1532. When elevated on a high sensitivity test, it reflects inflammation in the body. *See id.*

[37] Dermatofibroma is "a benign, circumscribed, red to brown nodule in the dermis . . . . It is a form of benign fibrous histiocytoma, and the two terms are sometimes used synonymously . . . ." *Dorland's* at 496.

In 2022, Petitioner underwent repeat antibody testing to attempt to establish an autoimmune etiology for her POF. On April 8, 2022, Petitioner's labs showed negative 21-hydroxylase,[38] thyroid peroxidase,[39] and thyroglobulin antibodies. Pet'r's Ex. 121 at 3, ECF No. 156-1. On August 19, 2022, Petitioner returned to dermatologist Dr. Garshick for her recurrent rashes. Pet'r's Ex. 123 at 6. Petitioner reported her chief complaint as "psoriasis, new growth on skin[.]" *Id.* Petitioner also reported psoriasis in her ears, flares on her scalp, and that she was being monitored for "nevus on [the right] medial thigh[.]" *Id.* Petitioner explained that her psoriasis had been present for "years" in her ears and on her scalp but was now "worsening" with itchiness, bleeding, and scaling/flaking. *Id.* at 8. Dr. Garshick's notations regarding the history of Petitioner's present illness reflect that Petitioner was mainly concerned about her scalp and that her condition was "staying the same[.]" *Id.* at 9. Dr. Garshick's assessment included psoriasis that was "established (worsening)[,]" and Petitioner was treated accordingly. *Id.*

Petitioner's relevant laboratory testing can be summarized as follows:

	12/16/2010	**7/27/2011**	**3/17/2012**	**2/5/2015**	**2/6/2017**	**4/8/2022**
ANA	Negative	Positive (1:160)	Negative	-	Positive (>1:80)	-
Anti-adrenal antibodies	-	-	Negative	Negative	-	Negative
Anti-ovarian antibodies	-	-	Negative	-	-	-
Thyroid peroxidase antibodies	-	-	Negative	-	-	Negative
Anti-thyroid globulin	-	-	Negative	-	-	Negative

See e.g., Pet'r's Ex. 137 at 3.

III. Expert Review[40]

A. Petitioner's Expert, David Axelrod, M.D.

[38] 21-hydroxylase antibodies refer to markers of autoimmune Addison's disease. *Dorland's* at 882. Addison's disease is "a chronic type of adrenocortical insufficiency, characterized by hypotension, weight loss, anorexia, weakness, and a bronzelike hyperpigmentation of the skin. It is due to tuberculosis- or autoimmune-induced destruction of the adrenal cortex, which results in deficiency of aldosterone and cortisol and is fatal in the absence of replacement therapy . . . . Called also *chronic adrenocortical insufficiency* and *primary adrenal* or *primary adrenocortical insufficiency." Id.* at 528.

[39] Thyroid peroxidase antibodies can be a sign of Hashimoto's thyroiditis, which is an autoimmune disease and most common cause of hypothyroidism. *Dorland's* at 102.

[40] This Decision is limited to a discussion of *Althen* prongs two and three and the expert reports authored in support thereof. I therefore do not find it necessary to re-address the reports authored in support of *Althen* prong one, or the qualifications of the experts that opined on that factor only, unless the expert also authored reports on prongs two and three. *See generally* Findings of Fact, ECF No. 147.

Dr. Axelrod received his medical degree from the University of Michigan Medical School in 1974. Pet'r's Ex. 125 at 1, ECF No. 164. Dr. Axelrod is a "[c]linical [i]mmunologist, trained at McGill University . . . and at the National Institutes of Health[.]" *Id.* The focus of his training at these institutions was in allergy and rheumatology. *Id.* He has held several academic appointments, including serving as the Academic Chief in the Division of Allergy, and later the Head of Clinical Research, at the Mount Carmel Mercy Hospital in Detroit, Michigan from 1984 to 1989, and then as an Associate Professor of Adult Rheumatology at the Medical College of Ohio until 1991. *Id.* at 2. He joined the faculty at New Jersey Medical School as an Associate Professor in the Division of Allergy, Immunology, and Rheumatology in 2007, and served as the Interim Director of the same division from 2009 until 2010. *Id.* During his clinical practice from 1991 until his retirement in 2018, he "was involved with the diagnosis and treatment of individuals with drug reactions (including to vaccines)." *Id.*; Pet'r's Ex. 124 at 1. He holds memberships in numerous medical societies related to allergy, immunology, and rheumatology. Pet'r's Ex. 125 at 2. His curriculum vitae contains approximately twenty-seven publications and abstracts of which he is a listed author. *See id.* at 3–4.

B. Petitioner's Expert, Orit Pinhas-Hamiel, M.D.

Dr. Pinhas-Hamiel received her medical degree from the Sackler School of Medicine at Tel-Aviv University in Israel in 1986. Pet'r's Ex. 18 at 1, ECF No. 59-6. She completed an internship and residency in pediatrics at Sheba Medical Center from 1985 to 1992. Pet'r's Ex. 137 at 1. Dr. Pinhas-Hamiel then completed a fellowship in pediatric endocrinology at the Children's Hospital in Cincinnati, Ohio in 1995. *Id.* She is board certified in pediatrics and pediatric endocrinology. *Id.* She has been Head of the National Juvenile Diabetes Center at Maccabi Health Care Services since 2000. Pet'r's Ex. 18 at 4. Dr. Pinhas-Hamiel has also been Head of the Endocrine and Diabetes Unit at Edmond & Lily Safra Children's Hospital, which is part of The Chaim Sheba Medical Center, in Israel since 2002. *Id.* She is the author or co-author of eighty-nine articles as well as numerous case reports, review articles, book chapters, and other works. *Id.* at 11–62. She has been a member of the editorial boards of Pediatric Diabetes and Frontiers in Endocrinology since 2011 and a member of the World Journal of Diabetes editorial board since 2014. *Id.* at 63. Dr. Pinhas-Hamiel noted that providing a "[w]ork-up diagnosis for amenorrhea . . . is a frequent problem [she] encounter[s] in [her] daily practice." Pet'r's Ex. 137 at 1.

C. Respondent's Expert, Thomas Forsthuber, M.D.

Dr. Forsthuber received medical and doctoral degrees from the University of Tübingen in Germany between 1987 and 1989. Resp't's Ex. B at 2, ECF No. 56. He completed post-doctoral programs at the University of Mainz in Germany, the University of California at Los Angeles's Department of Microbiology and Molecular Genetics, and Case Western Reserve University. *Id.* Dr. Forsthuber has been a Professor of Immunology in the University of Texas at San Antonio's Department of Biology since 2005. *Id.* at 2–3. He is also an Adjunct Professor of Pathology and of Microbiology & Immunology at the UT Health Sciences Center. *Id.* He currently serves in editorial positions on multiple journals, including, for example, *Clinical Immunology* as well as *Autoimmunity*. *Id.* at 10. He is a listed author on eighty-five articles and four book chapters as well as numerous abstracts. *Id.* at 19–27, 32–40. Much of Dr. Forsthuber's research is focused on autoimmunity and related topics. *See id.*

D. Respondent's Expert, Corinne Welt, M.D.

Dr. Welt received her medical degree from Cornell University Medical College in 1991. Resp't's Ex. O at 1, ECF No. 173-21. She completed post-doctoral training at the Brigham and Women's Hospital in internal medicine from 1991 to 1994. *Id.* Dr. Welt then completed fellowships in endocrinology and reproductive endocrinology at Massachusetts General Hospital and Harvard Medical School in 1997. *Id.* From there, she served on the faculty at Massachusetts General Hospital in the Reproductive Endocrine Unit. Resp't's Ex. N at 1, ECF No. 173-1. Dr. Welt has been a Professor of Internal Medicine (Endocrinology and Metabolism) at the University of Utah since 2014. Resp't's Ex. O at 1. She has served as the Chief of the Endocrinology, Metabolism, and Diabetes Division at the same institution since 2019. *Id.* Dr. Welt has held several editorial and reviewer positions on journals regarding reproduction, endocrinology, and metabolism. *Id.* She is also a member of numerous professional organizations and scientific activities related to endocrinology, POF, and infertility. *Id.* at 4–6. Dr. Welt's curriculum vitae lists over one hundred thirty-five articles, books, book chapters, and abstracts, of which she is a listed author. *Id.* at 9–25.

Dr. Welt's medical focus involves ovulatory disorders in women, including POI. Resp't's Ex. N at 1. She is currently a "key investigator [of POI,] coining the name change [from POF] . . . and leading [] research examining the etiology of POI and reviewing POI diagnostic criteria and treatment." *Id.* She actively serves as a treating physician in the field of reproductive endocrinology in Salt Lake City, UT. Resp't's Ex. O at 2. She has seen "over 100 women with POI" and has "identified the cause of POI in multiple women[.]" Resp't's Ex. N at 1.

IV. Expert Reports

A. David Axelrod, M.D.

Dr. Axelrod authored one written report in support of Petitioner's claim regarding *Althen* prongs two and three. Pet'r's Ex. 124. Dr. Axelrod did not dispute Petitioner's POI diagnosis and deferred to the treater who made this evaluation. *Id.* at 4. Dr. Axelrod's description of Petitioner's history was generally consistent with her medical records.[41] *See id.* at 1–4. He described the logical sequence of cause and effect in Petitioner's case and argued that following Petitioner's June 4, 2010 Gardasil vaccination, she "developed a protective immune response to the components of the [] vaccine[,]" causing her to develop autoimmune POI. *Id.* at 7.

Specifically, Dr. Axelrod opined that given Petitioner's family history of autoimmunity (scleroderma), her detectable positive ANAs, and her psoriasis diagnosis, "it is likely that [Petitioner's] immune cells [] had escaped central selection and were held at bay by peripheral positive selection (regulation)." *Id.* He continued, "then with the Gardasil injection, she lost the positive selection (regulation) of her autoreactive immune cells that were then activated by the

[41] Dr. Axelrod wrote that Petitioner had a positive ANA on July 31, 2011. Pet'r's Ex. 124 at 2 (citing Pet'r's Ex. 9 at 72–76). However, it appears Petitioner's date of testing and positive ANA screening occurred on July 27, 2011. Pet'r's Ex. 9 at 7. Additionally, Dr. Axelrod wrote that Petitioner had another positive ANA screening on October 14, 2011. Pet'r's Ex. 124 at 3 (citing Pet'r's Ex. 3 at 1). This notation seems to be a reiteration of Petitioner's positive ANA on July 27, 2011. *See* Pet'r's Ex. 3 at 1; Pet'r's Ex. 9 at 72–76.

vaccine and attacked her ovaries," resulting in POI. *Id.* Dr. Axelrod explained, consistent with my ruling on *Althen* prong one, that such activation occurred because of "similar amino acid sequences between the Gardasil vaccine components and [Petitioner's] autoantigen targets of her ovaries." *Id.* at 8. This degree of similarity "allow[ed] those cells to avoid her immune regulatory networks for the ovary directed immune cells." *Id.* Dr. Axelrod argued that while such autoreactive immune cells typically "participate[] in the protective effects of the Gardasil vaccine," they also "attacked and damaged" Petitioner's ovaries, causing her autoimmune POI. *Id.*

Dr. Axelrod "support[ed] the molecular mimicry [theory] outlined . . . by Dr. Shoenfeld [in the ruling on *Althen* prong one] that was shown to be sound and reliable[.]" *Id.* at 6. However, Dr. Axelrod added additional homologies "that [he argued] bolster the role of molecular mimicry and cross-reactivity in the development of [Petitioner's POF]." *Id.* Specifically, Dr. Axelrod reiterated that the Gardasil vaccine Petitioner received contains the L1 protein from the following strains: HPV 6, 11, 16, 18. *Id.* Relying on the Tuohy and Altuntas[42] review noting that MATER and α-enolase are the target antigens for autoimmune POI, Dr. Axelrod assessed and documented several "antigen peptide alignments[]" between such target antigens and strains within the HPV vaccine Petitioner received. *Id.* at 7 (citing Pet'r's Exs. 133–36, ECF Nos. 165-8–165-11; Resp't's Ex. K, Tab 9, ECF No. 138-9). To arrive at such conclusion, Dr. Axelrod ran searches through a "clustal program" and noted that the L1 protein from HPV strain 6 and MATER "share amino acid sequences of 3–10 conserved similar conserved amino acids." *See id*. Likewise, the same HPV strain compared to α-enolase share 3–7 amino acids. *Id.* Dr. Axelrod also compared the HPV 6 L1 peptide with α-enolase and keratin 17, the autoantigen thought to be targeted in psoriasis. *Id.*; *see also* Pet'r's Ex. 126, ECF No. 165-1.[43] He found 3 shared amino acids. *Id.* Dr. Axelrod found the same number of homologies in his comparison of the L1 protein of HPV 6, MATER, and keratin 17. Pet'r's Ex. 124 at 7. Dr. Axelrod then argued that the methods used to measure α-enolase and/or MATER autoantibodies "are not currently used in clinical practice." *Id.* at 5. He continued, "[t]herefore, even if [Petitioner] had antibodies or cells to these presumed target antigens in POF, they were not sought by her physicians." *Id.*

He addressed the lack of positive autoantibodies in Petitioner, aside from her positive ANA. *Id.* Dr. Axelrod argued that "it is unlikely that every subject with an autoimmune POF will have an associated autoimmune disorder or antibodies." *Id.* Dr. Axelrod cited a review by La Marca et al.[44] to argue that it is not significant that Petitioner did not "have detectable multiple autoantibodies." *Id.* at 6 (citing Resp't's Ex. K, Tab 6 at 3–6, ECF No. 138-6). La Marca et al. tabulated the frequency of ovarian antibodies to certain "steroidogenic enzymes" in patients with POI. Resp't's Ex. K, Tab 6 at 3. The authors found that among their isolated POI patients, and their POI patients with a comorbid autoimmune disease who did not have adrenal insufficiency, antibodies to steroid-cell autoantibodies, were found in less than 5% of the patients. *Id.* However, they found that "more relevant" is the association between POI and autoimmune Addison's disease, because "[a]pproximately 4–8% of women with POI are positive for circulating adrenal

[42] V. Tuohy & C. Altuntas, *Autoimmunity and premature ovarian failure,* 19 CURR. OPIN. OBSTET. GYNECOL. 366–69 (2007).
[43] Y. Liang et al., *Psoriasis: A mixed autoimmune and autoinflammatory disease,* 49 CURR. OPIN. IMMUNOL. 1–8 (2017).
[44] A. La Marca et al., *Primary ovarian insufficiency: autoimmune causes,* 22 CURR. OPIN. OBSTET. GYNECOL. 277–82 (2010).

autoantibodies[.]" *Id.* at 2. The authors determined that ovarian autoantibodies against steroidogenic enzymes are present "almost exclusively in women with clinical or preclinical [autoimmune Addison's disease]." *Id.* at 3. La Marca et al. wrote that the absence of such autoantibodies "does not exclude the possibility that other auto-antibodies may be present and other autoimmune mechanisms may be active[]" in the development of POI. *Id.* at 4. Dr. Axelrod therefore argued that while Petitioner did not have multiple, detectable autoantibodies, the La Marca et al. study says she would not have been expected to have "multiple" autoantibodies, "given that she did not have autoimmune adrenal insufficiency." Pet'r's Ex. 124 at 6.

Dr. Axelrod described the accepted timeframe for a primary adaptive immune response to occur following vaccination. *Id.* at 8. He argued that such a response occurs within two weeks. *Id.* He cited a book chapter by Abbas et al.[45] entitled "Properties and Overview of Immune Responses." *Id.* (citing Pet'r's Ex. 130, ECF No. 165-5). Dr. Axelrod relied on this overview to illustrate that a primary adaptive immune response "may peak by 14 days following an initial exposure to [an] antigen." *See id.* He further relied on "an observational study [by Lawley et al.] of subjects with an autoimmune disorder[,]" serum sickness.[46] *Id.* at 9 (citing Pet'r's Ex. 131 at 1, ECF No. 165-6).[47] Lawley et al. "prospectively evaluated the clinical and immunologic features of serum sickness" in twelve children. Pet'r's Ex. 131 at 1. As part of their evaluation, the authors observed the time it took for child subjects to develop a primary adaptive immune response after being treated with horse anti-thymocyte globulin. *Id.* The authors noted that manifestations of a primary adaptive immune response occurred from ten to twenty-five days following exposure to the antigen. *Id.* at 2–4. The authors determined that symptoms of the disease occurred around the time of the peak immune response within this timeframe. *See id.*

Regarding Petitioner, Dr. Axelrod noted that Petitioner received her first dose of the HPV vaccine on June 4, 2010, and argued that her menstrual cycle ceased after August 1, 2010. Pet'r's Ex. 124 at 9 (citing Pet'r's Ex. 12 at 2). He continued that by August 6, 2010, Petitioner exhibited FSH and LH levels in the postmenopausal range, and she had been experiencing hot flashes for the past two weeks. *Id.* (citing Pet'r's Ex. 2 at 50–52, 59). Dr. Axelrod stated that "[t]his would put the onset of her symptoms that lead to her diagnosis of [POI] on or about July 23, 2010." *Id.* However, Dr. Axelrod opined that "[i]t is likely that the disease process began sometime prior to July 23, 2010, to result in her symptoms[]" by that date. *Id.* He posited that if the damage did not begin closer in time to Petitioner's June 4, 2010 HPV vaccine, her symptoms "could not have occurred" by July 23, 2010. *Id.* at 10. However, Dr. Axelrod did not identify the date of onset in more detail. *See id.* at 9.

[45] ABUL K. ABBAS et al., CELLULAR & MOLECULAR IMMUNOLOGY 1–11 (Elsevier eds., 9th ed. 2018).

[46] Serum sickness is "a hypersensitivity reaction to the administration of foreign serum or serum proteins characterized by fever, urticaria, arthralgia, edema, and lymphadenopathy. It is caused by the formation of circulating antigen-antibody complexes that are deposited in tissues and trigger tissue injury mediated by complement and polymorphonuclear leukocytes." *Dorland's* at 1707.

[47] T. Lawley et al., *A Prospective Clinical and Immunologic Analysis of Patients with Serum Sickness,* 311:22 N. ENG. J. MED. 1407–14 (2011).

To explain the apparent inconsistency between the onset of Petitioner's POI and the cited literature regarding an immune-mediated response, Dr. Axelrod relied on a study by Herrin et al.[48] *Id.* at 10 (citing Pet'r's Ex. 132, ECF No. 165-7). Herrin et al. observed the antibody response to two different trademarked HPV vaccinations (Gardasil and Cervarix), using data from the Vaccine Research Center. *See* Pet'r's Ex. 132. The authors found that antibody levels following either HPV vaccine began to increase one month post vaccination, peaked around seven months post vaccination, and that antibodies were still present twenty-four months post vaccination. *Id.* at 3. They noted, however, that the patients they observed had received a second and third dose of the vaccine after one and six months, respectively. *See id.* Since Petitioner only received one dose of the vaccine, Dr. Axelrod insinuated that the peak immune response and manifestation of her POI would be expected to be less than the patients in the Herrin et al. study. Pet'r's Ex. 124 at 10. Relying on the Herrin et al. study, he opined that the "time interval between [Petitioner's] first Gardasil injection and the onset of her first symptom of what became her [POI] is consistent with a primary adaptive response to the [vaccine] that she received on June 4, 2010." *See id.*

Dr. Axelrod addressed a potential autoimmune comorbidity in Petitioner's case and argued that Petitioner also suffers from psoriasis. *Id.* at 4. As support for Petitioner's psoriasis diagnosis, Dr. Axelrod cited Petitioner's visit notes with a dermatologist on August 19, 2022, which listed psoriasis as a diagnosis. *Id.* (citing Pet'r's Ex. 123 at 9). He also cited to Dr. Reddy's March 28, 2013 visit notes, made closer in time to Petitioner's purported development of POI, wherein Dr. Reddy identified a differential diagnosis of either eczema or psoriasis. *Id.* (citing Pet'r's Ex. 6 at 1–3).

Dr. Axelrod submitted medical literature to show that psoriasis is thought to be an autoimmune disease. *Id.* He cited an article by Liang et al.,[49] which "proposed that autoimmune and autoinflammatory processes contribute to the development of [p]soriasis." *See* Pet'r's Ex. 126 at 1. They noted this is because both adaptive immune responses and innate responses are involved in the development of varying types of psoriasis. *Id.* The authors wrote that "[t]he balance between the two dictate the clinical presentation of psoriasis with chronic plaque psoriasis having prominent adaptive/autoimmune responses[,] while pustular psoriasis is dominated by autoinflammatory immune responses." *Id.* at 1, 3. Liang et al. found that peptides from keratin 17, "[t]he antimicrobial peptide LL-37[,]" and "the ADAMTS-like protein 5 []" are the autoantigens (targets) responsible for the development of psoriasis. *Id.* at 4. Dr. Axelrod used the authors' findings to support his argument that psoriasis is an autoimmune disease and Petitioner therefore suffered from another autoimmune disorder. Pet'r's Ex. 124 at 4 (citing Pet'r's Ex. 126).

He also cited an Indian Dermatology Online Journal study by Vashist et al.,[50] which noted "[p]soriasis, an immune-mediated inflammatory dermatosis, . . . has been widely viewed as an autoimmune disease . . . triggered . . . by molecular mimicry." *Id.* (citing Pet'r's Ex. 127 at 1, ECF No. 165-2). Vashist et al. not only indicated that psoriasis itself is an autoimmune disease, they

[48] D. Herrin et al., *Comparison of adaptive and innate immune responses induced by licensed vaccines for Human Papillomavirus,* 10:12 HUM. VACC. & IMMUNOTHERAPEUT. 3446–54 (2014).
[49] Y. Liang et al., *Psoriasis: A mixed autoimmune and autoinflammatory disease,* 49 CURR. OPIN. IMMUNOL. 1–8 (2017).
[50] S. Vashist et al., *Association of Psoriasis with Autoimmune Disorders: Results of a Pilot Study,* 11 INDIAN DERMATOL. ONLINE J. 753–59 (2020).

also investigated the association of psoriasis with other autoimmune disorders. Pet'r's Ex. 127 at 1. The authors studied eighty psoriasis patients (fifty-seven males and twenty-three females), aged 13–75 years, for "concurrent autoimmune disorders." *Id.* Of the eighty patients, thirty-seven of them (46.3%) "had clinical and/or sero-abnormality suggestive of autoimmune disorders[.]" *Id.* Specifically, they noted that 3.8% had vitiligo,[51] 1.3% had type-1 diabetes mellitus,[52] and 6.3% had type-2 diabetes mellitus. *Id.* The authors also found that "[s]ero-positivity reflecting subclinical autoimmunity was noted for anti-CCP antibodies (in 2.5%), rheumatoid factor (in 2.5%), hypo- or hyper-thyroidism (in 8.8%), anti-TPO antibodies (in 5.0%), anti-tTG antibody (in 1.3%), ANA (in 5.0%), anti-dsDNA antibody (in 2.5%), and anti-Ro antibody in 11.3% patients." *Id.* They also found elevated fecal calprotectin levels suggestive of inflammatory bowel disease ("IBD")[53] in 11.2% of patients. *Id.* The authors determined that "psoriasis patients seem to have a predilection for other autoimmune disorders, particularly vitiligo, diabetes mellitus, autoimmune thyroiditis, rheumatoid arthritis ("RA"),[54] and IBD. *Id.* However, they concluded that the "association between psoriasis and other autoimmune disorders at best remains tenuous for want of strong evidence." *Id.*

B. Orit Pinhas-Hamiel, M.D.

Dr. Pinhas-Hamiel submitted one written report specifically on *Althen* prongs two and three, in addition to her earlier reports drafted generally in support of Petitioner's claim. *See* Pet'r's Ex. 17, ECF No. 59-5; Pet'r's Ex. 27, ECF No. 98-2; Pet'r's Ex. 91, ECF No. 122-1; Pet'r's Ex. 137. Dr. Pinhas-Hamiel wrote "there is no doubt about the diagnosis of ovarian failure." Pet'r's Ex. 137 at 3. She posited that since there is no doubt about Petitioner's POF diagnosis, "[t]he question is, what went wrong in a fully pubertal woman who had two spontaneous pregnancies?" *Id.*

Dr. Pinhas-Hamiel attributed Petitioner's POI to her June 4, 2010 HPV vaccination and opined that Petitioner's POI is autoimmune in nature.[55] *Id.* at 4. As support, Dr. Pinhas-Hamiel

[51] Vitiligo is "1. a chronic, usually progressive, type of hypomelanosis in which melanocytes are destroyed, resulting in white patches on the skin that may be surrounded by a hyperpigmented border; there is an autosomal dominant predisposition to the condition, and the etiology is thought to be an autoimmune mechanism. 2. depigmentation." *Dorland's* at 2069.

[52] Type-1 diabetes mellitus is "one of the two major types of diabetes mellitus: an autoimmune disease that results in the destruction of beta cells of the pancreas, leading to loss of the ability to secrete insulin. It is characterized by an abrupt onset of symptoms, insulinopenia, and dependence on exogenous insulin to sustain life; peak age of onset is 12 years, although onset can be at any age." *Dorland's* at 506.

[53] Inflammatory bowel disease is "a general term for those inflammatory diseases of the intestines that have an unknown etiology, including Crohn disease and ulcerative colitis." *Dorland's* at 536.

[54] Rheumatoid arthritis is "a chronic systemic disease primarily of the joints, usually polyarticular, marked by inflammatory changes in the synovial membranes and articular structures and by muscle atrophy and rarefaction of the bones. In late stages, deformity and ankylosis develop. The cause is unknown, but autoimmune mechanisms and virus infection have been postulated." *Dorland's* at 150.

[55] I must note that Dr. Pinhas-Hamiel's first expert report drafted in 2015 appears to be similar to her latest report drafted in 2022. *See* Pet'r's Ex. 17; *see also* Pet'r's Ex. 137. Yet, in Dr. Pinhas-Hamiel's first report, she addressed autoimmunity as an etiology of POI generally, and in Petitioner's case. Pet'r's Ex. 17 at 5. She opined that there was no evidence of autoimmunity in Petitioner's case because "[a]lthough [Petitioner

noted that Petitioner's genetic testing was normal.[56] *Id.* (citing Pet'r's Ex. 13; Pet'r's Ex. 5 at 52). She also noted that Petitioner had a positive ANA on July 27, 2011, approximately one year after her June 4, 2010 vaccination. *Id.* at 6. Dr. Pinhas-Hamiel opined that supplemental support for an autoimmune etiology is found in the fact that Petitioner experienced one additional positive ANA in 2017. *Id.* at 11.

Additionally, Dr. Pinhas-Hamiel argued the timeframe for the onset of Petitioner's pre-menopausal symptoms and bloodwork consistent with POI six weeks post Gardasil vaccination fits within the accepted timeframe for the onset of an autoimmune disease. *Id.* Dr. Pinhas-Hamiel wrote that although the onset of pre-menopausal symptoms can vary, "a few weeks is consistent with an immune mediated response and subsequent hormonal changes resulting in" autoimmune POI. *Id.* She therefore maintained that it is "more probable than not that the cause of [Petitioner's POF] is secondary to [an] immune response secondary to the Gardasil vaccine." *Id.* at 12. Dr. Pinhas-Hamiel argued that given the lack of evidence for any alternative cause for Petitioner's POI, her vaccine must have been responsible for her ovarian failure. *Id.* at 9.

She wrote that currently, "there is no proven sensitive and specific serum test to confirm that a woman has ovarian failure on an autoimmune basis." *Id.* at 6 (citing Pet'r's Exs. 138–39, ECF Nos. 171-1–171-2).[57] However, Dr. Pinhas-Hamiel then wrote that "[a]utoantibodies are a hallmark of autoimmunity" and that autoantibodies like ANAs "have a central role" in identifying autoimmune etiology. *Id.* Dr. Pinhas-Hamiel argued that the presence of ANAs suggests the presence of autoimmune disease, specifically "systemic autoimmune rheumatic disease[s], such as systemic lupus erythematosus [("SLE")].[58]" *Id.* While Dr. Pinhas-Hamiel wrote that a positive ANA is associated with autoimmune disease, she admitted that "[s]ome individuals . . . may have a positive test for ANA and yet never develop any autoimmune disease." *Id.* at 8.

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had] family history of . . . autoimmune disorder . . . there were no signs of autoimmune disorders such as hypo or hyperthyroidism, there were no antibodies to the thyroid gland, to the ovaries[,] or to the adrenals." *See id.* Now, she argues there is evidence of autoimmunity in Petitioner's case. Pet'r's Ex. 137 at 4.

[56] Dr. Pinhas-Hamiel wrote that Turner syndrome, or the lack of a second X chromosome, is the most common cause of POI. Pet'r's Ex. 137 at 4. He posited that Petitioner's karyotype results to test for Turner syndrome were pending as of September of 2022. *Id.* However, this appears to be inaccurate. Petitioner's testing revealed a normal female karyotype on October 10, 2014. *See* Pet'r's Ex. 13 at 2. Petitioner's other expert, Dr. Axelrod, even noted this fact. *See* Pet'r's Ex. 124 at 3. Petitioner's records do not contain any evidence that she suffers from Turner syndrome.

[57] J. Novosad et al., *Ovarian antibodies as detected by indirect immunofluorescence are unreliable in the diagnosis of autoimmune premature ovarian failure: a controlled evaluation,* 3:2 BMC WOMEN'S HEALTH 1–7 (2003); A. Szeliga et al., *Autoimmune Diseases in Patients with Premature Ovarian Insufficiency – Our Current State of Knowledge,* 22 INT. J. MOL. SCI. 1–11 (2021).

[58] Systemic lupus erythematosus is "a chronic, inflammatory, often febrile multisystemic disorder of connective tissue that proceeds through remissions and relapses; it may be either acute or insidious in onset and is characterized principally by involvement of the skin . . . joints, kidneys, and serosal membranes. The etiology is unknown, but it may be a failure of regulatory mechanisms of the autoimmune system, since there are high levels of numerous autoantibodies against nuclear and cytoplasmic cellular components." *Dorland's* at 1080.

As support, she cited a study by Miyake et al.[59] that "assess[ed] 20 women with secondary amenorrhea manifesting hormonal and clinical features of [POF] by different kinds of circulating autoantibodies[.]" *Id.* at 6 (citing Pet'r's Ex. 146 at 1, ECF No. 171-9). The authors found that "35% had anti-thyroglobulin antibodies, 30% had anti-parietal cell antibodies, and 40% had [ANA]." *See id.* Dr. Pinhas-Hamiel pointed out that in some cases in the study, ANA was the only positive antibody. Pet'r's Ex. 137 at 6. She argued that since anti-adrenal antibodies were negative in all patients, adrenal antibodies are not necessary for the diagnosis of POI, but rather a positive ANA is required. *Id.* She also cited a study by Ishizuka et al.[60] that observed thirty-two women with POI with and without chromosomal abnormalities. Pet'r's Ex. 140 at 1, ECF No. 171-3. The authors found a positive ANA in 77% of them; however, this statistic was based on a subset of the study (thirteen patients) who had normal karyotypes and developed amenorrhea at or under the age of 30. *Id.* The authors did not make the same finding in patients who developed amenorrhea later in life. *Id.* They concluded that their results "suggest that patients with [POF] and ANA are an aetiologically [sic] and clinically distinct group." *See id.*

A study by Cameron et al.[61] relied upon by Dr. Pinhas-Hamiel found that among seventeen non-chromosomal, non-iatrogenic, adolescent POI patients, 41.1% were positive for ANAs. Pet'r's Ex. 137 at 7 (citing Pet'r's Ex. 141 at 1, ECF No. 171-4). The authors relied on this finding to argue that a positive ANA is evidence of autoimmunity in POI. Pet'r's Ex. 141 at 2, 4. However, they noted that the "clinical significance of this [finding] is unknown because estimates of ANA positivity in healthy individuals range from 5 to 30% in adults . . . ." *Id.* at 4. They also indicated that low ANA titers (1:160 or less) are even less likely to be clinically significant and that only three patients in their study had "high ANA titers that may be associated with autoimmune disease." *Id.* at 2. Such patients had titers greater than 1:1280. *Id.* Dr. Pinhas-Hamiel finally cited a study by Zhen et al.[62] that examined ninety-six patients with POF compared to one hundred healthy controls. Pet'r's Ex. 137 at 7 (citing Pet'r's Ex. 142, ECF No. 171-5). The authors found that 19.8% and 14% of patients, respectively, had positive ANA titers. *See id.* However, the authors noted this finding "did not reach statistical significance." Pet'r's Ex. 142 at 4. Dr. Pinhas-Hamiel argued based on the medical literature that a positive ANA result "suggests the presence of autoimmune disease[.]" Pet'r's Ex. 137 at 7.

Dr. Pinhas-Hamiel discussed the difficulty in standardizing the ANA titer used between laboratories to address Petitioner's fluctuating ANAs. *Id.* Dr. Pinhas-Hamiel noted that when patients' samples are tested at a dilution of 1:40, "[t]his standardization makes the ANA test very sensitive for the diagnosis of autoimmune diseases but results in many false positive results." *Id.* She explained that this is because "[i]mmunoassays [used to measure the presence of ANAs] are well known to be prone to interferences due to the complexity of antigen-antibody interaction and

[59] T. Miyake et al., *Implications of circulating autoantibodies and peripheral blood lymphocyte subsets for the genesis of premature ovarian failure,* 12(3) J. REPROD. IMMUNOL. 163–71 (1987).
[60] B. Ishizuka et al., *Anti-nuclear antibodies in patients with premature ovarian failure,* 14:1 HUM. REPROD. 70–75 (1999).
[61] M. Cameron et al., *Non-Chromosomal, Non-Iatrogenic Premature Ovarian Failure in an Adolescent Population: A Case Series,* 21 J. PEDIATR. ADOLESC. GYNECOL. 3–8 (2008).
[62] X. Zhen et al., *Serologic autoimmunologic parameters in women with primary ovarian insufficiency,* 15:11 BMC IMMUNOL. 1–6 (2014).

low concentration of an analyte." *Id.* at 8. She noted false results can also be due to inconsistencies caused by using different labs. *Id.*

Dr. Pinhas-Hamiel relied on the Pashnina et al.[63] review of the role of positive ANAs in autoimmunity and wrote that at a dilution of 1:40, 20 to 30% of healthy patients have a positive ANA. *Id.* (citing Pet'r's Ex. 143 at 9, ECF No. 171-6). She noted the authors' findings showed that testing at a dilution of 1:80 reveals a positive ANA in 10 to 12% of healthy individuals. *See id.* She continued that a dilution of 1:160 shows a positive ANA in only 5% of healthy individuals. *Id.* Pashnina et al. wrote that studies have shown that "the positive predictive value of ANAs for the diagnosis of [autoimmune diseases] with the 1:160 cut-off titer was 11.6%." Pet'r's Ex. 143 at 11. The authors noted that even in the diagnosis of certain autoimmune diseases, such as SLE, that are known to have a higher significance of ANAs, the diagnostic value of ANAs still does not exceed 15%. *Id.* Pashnina et al. acknowledged that ANAs are known to be detected in systemic autoimmune diseases, including scleroderma, Sjögren's syndrome,[64] mixed connective tissue disease,[65] RA, hepatitis, Hashimoto's thyroiditis, immune thrombocytopenic purpura,[66] idiopathic epilepsy, ischemic brain disease,[67] and interstitial lung disease.[68] *Id.* at 7. Dr. Pinhas-Hamiel relied on Pashnina et al.'s findings and argued that testing at a 1:160 dilution "increases the specificity of the ANA test for the diagnosis of autoimmune diseases" such as POI. Pet'r's Ex. 137 at 7. She noted that Petitioner's ANA testing showed a positive titer at 1:160. *Id.* at 8.

She addressed the "fluctuation" in Petitioner's antibody levels, specifically the fact that a positive ANA was not consistently detected in Petitioner. *Id.* Dr. Pinhas-Hamiel relied on the descriptions in the Pashnina et al. article and argued that patients with autoimmune diseases may show a "decrease in the level of certain autoantibodies and/or the strength of antibody-mediated bioeffects in comparison with healthy donors." *Id.* (citing Pet'r's Ex. 143 at 3). The authors noted

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[63] I. Pashnina et al., *Antinuclear Autoantibodies in Health: Autoimmunity is Not a Synonym of Autoimmune Disease,* 10 ANTIBODIES 1–26 (2021).

[64] Sjögren's syndrome is "a symptom complex of unknown etiology, usually occurring in middle-aged or older women, marked by the triad of keratoconjunctivitis sicca with or without lacrimal gland enlargement, xerostomia with or without salivary gland enlargement, and the presence of a connective tissue disease, usually rheumatoid arthritis but sometimes systemic lupus erythematosus, scleroderma, or polymyositis. An abnormal immune response has been implicated." *Dorland's* at 1848.

[65] Mixed connective tissue disease is "a disorder combining features of scleroderma, myositis, systemic lupus erythematosus, and rheumatoid arthritis, and marked serologically by the presence of antibody against extractable nuclear antigen." *Dorland's* at 539.

[66] Immune thrombocytopenic purpura is "any form of purpura in which the platelet count is decreased; it may be either *primary* or *secondary.*" *Dorland's* at 1557. Purpura refers to "1. any of a group of conditions characterized by ecchymoses or other small hemorrhages in the skin, mucous membranes, or serosal surfaces; causes include blood disorders, vascular abnormalities, and trauma. 2. any of several conditions similar to the traditional purpura group, which may be caused by decreased platelet counts, platelet abnormalities, vascular defects, or reactions to drugs." *Id.*

[67] Ischemic brain disease, also called cerebral ischemia, is the "deficiency of blood in [the brain], usually due to functional constriction or actual obstruction of a blood vessel." *Dorland's* at 536.

[68] Interstitial lung disease is "a heterogeneous group of noninfectious, nonmalignant disorders of the lower respiratory tract, affecting primarily the alveolar wall structures but also often involving the small airways and blood vessels of the lung parenchyma; slowly progressive loss of alveolar-capillary units may lead to respiratory insufficiency and death." *Dorland's* at 536.

that a growing number of studies show that the "level of autoantibodies decreases, rather than increases during exacerbations of some [autoimmune diseases]" described above. Pet'r's Ex. 143 at 3. Pashnina et al. wrote that this fact is applicable to autoantibodies such as ANAs. *Id.* The authors analogized ANAs and antibodies relevant to endocrine disorders and noted that while "[t]raditionally, it was assumed . . . that the more autoantibodies [] a patient has, the more symptoms of the disease that will be present[,]" it has now been suggested that "not only an increase, but also a pathological decrease in the concentration of autoantibodies may reflect and even cause pathological processes in the body." *Id.* However, the authors also acknowledged that "[a]ccording to the current opinion, ANAs . . . belong to the integral part of the normal functioning of the immune system." *Id.*

C. Thomas Forsthuber, M.D.

Dr. Forsthuber authored one written report refuting Petitioner's arguments regarding an autoimmune etiology for her POI. Resp't's Ex. M. Dr. Forsthuber deferred to Dr. Welt, Respondent's second expert, on the diagnosis of Petitioner's POI, but he opined that there is no reliable evidence for an autoimmune etiology. *Id.* at 6.

As support, Dr. Forsthuber summarized Petitioner's autoimmune laboratory testing and opined that when "[t]aken together, [Petitioner] does not have laboratory evidence of autoimmune POI." *Id.* at 5. Specifically, he wrote that Petitioner was tested on several occasions post vaccination for ovarian, adrenal, and thyroid autoantibodies "and the results were consistently negative." *Id.* Dr. Forsthuber also highlighted that Petitioner did not have other inflammatory markers, such as ESR and CRP, which, if abnormal, would show evidence of an autoimmune etiology. *Id.* at 19. Without such evidence, Dr. Forsthuber argued that Dr. Axelrod's theory of cause and effect is "not logical." *Id.* at 13. He pointed out Dr. Axelrod's acknowledgement that Petitioner does not have autoantibodies found in autoimmune POI cases, but he "interpret[ed] that lack of these autoantibodies as evidence that her POI is 'most likely of autoimmune origin.'" *Id.* (citing Pet'r's Ex. 124 at 6). Dr. Forsthuber posited that "the most likely explanation" for Petitioner's lack of autoantibodies, is that she does not have autoimmune POI. *Id.* (citing Pet'r's Ex. 5 at 33).

He also condemned Dr. Axelrod's reliance on Petitioner's treater Dr. Gleicher's notation indicating that Petitioner "likely had autoimmune POF." *Id.* at 6. Dr. Forsthuber argued that Dr. Gleicher did not have an account of Petitioner's full condition when documenting this opinion. *Id.* Rather, only after noting his opinion regarding autoimmunity did Dr. Gleicher order a "battery of laboratory tests including a 'full immunology' screen[.]" *Id.* at 6–7. Dr. Forsthuber indicated that the autoimmune workup, once performed, showed that Petitioner did not have anti-ovarian, anti-adrenal, 21-hydroxylase, or thyroid autoantibodies. *Id.* at 7. She also did not have evidence of another autoimmune condition. *Id.* Based on such findings, Dr. Forsthuber opined that "it is highly unlikely that Dr. Gleicher would maintain an opinion of autoimmune POI after obtaining these lab tests." *Id.*

Dr. Forsthuber acknowledged that Petitioner had fluctuating positive and negative testing for ANAs, but he found such findings insignificant. *Id.* at 6. For example, Petitioner's positive ANA test on February 6, 2017, was unsupported according to Dr. Forsthuber because all other

testing for autoimmune conditions performed that day was negative. *Id.* at 7. Dr. Forsthuber further argued that this finding is "of questionable relevance, especially in light of the fact that [Petitioner] had several ANA tests that were negative closer in time to [her June 4, 2010] vaccination[,]" including during December of 2010. *Id.* at 7, 19 (citing Pet'r's Ex. 2 at 42).

He also cited medical literature to support his opinion that Petitioner's positive ANA results are insignificant. Bloch et al. wrote that approximately 5% of healthy individuals have a positive ANA at a dilution of 1:160. *Id.* at 7 (citing Resp't's Ex. M1, ECF No. 172-2).[69] Bloch et al. noted that a positive ANA "may assist in the diagnosis of autoimmune diseases[]" and that a negative ANA decreases the likelihood that a patient's symptoms are caused by an autoimmune condition. Resp't's Ex. M1 at 1–2. They went on to list autoimmune conditions where patients are known to test positive for ANAs, including SLE, scleroderma, Sjögren's syndrome, mixed connective tissue disease, polymyositis, RA, thyroid diseases, gastrointestinal ("GI") diseases such as IBD, and pulmonary diseases. *Id.* at 2–3. Having one or more relatives with an autoimmune disease has also been known to be associated with positive ANA tests. *Id.* at 3. However, the authors wrote that some individuals, even without a relative with an autoimmune disease, "may have a positive test for ANA and yet never develop any autoimmune disease." *Id.* Bloch et al. issued a "word of caution" and indicated that a positive ANA "does not, by itself, indicate the presence of an autoimmune disease." *Id.* at 4. Rather, "many normal individuals will have a positive test at low titers [and e]ven when detected at high titer, a positive ANA result," in the absence of other symptoms or physical findings, "does not indicate that a patient has, or will develop, an autoimmune disease." *Id.* Dr. Forsthuber argued that based on Petitioner's history of negative ANAs and lack of other clinical evidence of autoimmunity, "it is highly likely" that her positive ANAs were false positives and therefore did not provide evidence of an autoimmune etiology. Resp't's Ex. M at 7.

Next, Dr. Forsthuber disputed Dr. Axelrod's explanation of molecular mimicry and argued that his proposed sequence homologies do not add support for an autoimmune etiology in Petitioner. *See id.* at 8. Specifically, Dr. Forsthuber argued that Dr. Axelrod "mistakes sequence homology with molecular mimicry." *Id.* at 9. He opined that "[a]mino acid homologies between viral and bacterial proteins and human proteins is the rule, and not the exception." *Id.* Furthermore, finding sequence homology between two random proteins can occur by "chance alone." *Id.* at 14–15. He continued that even if one finds a meaningful sequence homology, "this is not sufficient to claim that this sequence would be likely to induce autoimmune disease by way of molecular mimicry." *Id.* at 9. Dr. Forsthuber argued that many additional steps and testing would be required to reach such a conclusion, including BLAST searches, which Dr. Axelrod did not use. *Id.* at 9, 16–18. Instead, Dr. Axelrod used clustal searches. *See id.* at 9.

Dr. Forsthuber undertook a lengthy discussion[70] of Dr. Axelrod's "misconceptions about sequence alignments, [] fundamental mistakes in how to use the [c]lustal program, and []

[69] D. Bloch et al., *Patient education: Antinuclear antibodies (ANA) (Beyond the Basics),* UPTODATE, https://www.uptodate.com/contents/antinuclear-antibodies-ana-beyond-the-basics (last visited Jan. 31, 2023).

[70] Throughout this discussion, Dr. Forsthuber attacked Dr. Axelrod's accepted sequence length reflective of a molecular mimic. Resp't's Ex. M at 9. He cited medical literature attempting to refute that a short chain

misinterpretation of his clustal results[.]" *Id.* He criticized Dr. Axelrod's misapplication of the clustal omega tool and wrote that it is "not recommended for comparing two proteins such as NALP5/MATER or α-enolase with HPV L1 protein." *Id.* at 14. Because this program is not meant for comparing only two proteins, Dr. Forsthuber argued that Dr. Axelrod's conclusions are "unreliable." *Id.* Due to Dr. Axelrod's misuse and misinterpretation of the clustal tool, Dr. Forsthuber closely examined Dr. Axelrod's provided printouts and determined that Dr. Axelrod did not find amino acid sequences of 3–10 or 3–7 conserved similar amino acids as he claimed. *Id.* at 14 (citing Pet'r's Ex. 124 at 7; Pet'r's Exs. 133–36). He even noted that Dr. Axelrod's printouts "where he colored regions that he alleges to be similar," did not include an interpretation of the clustal results from the clustal software itself. *Id.* at 18 (citing Pet'r's Exs. 133–36). Instead, according to Dr. Forsthuber, Dr. Axelrod was responsible for coloring in the regions, based on "his misguided interpretation of the results." *See id.* Out of all four exhibits, Dr. Forsthuber found only one region where three amino acids overlap and that was between HPV L1 and α-enolase. *Id.* (citing Pet'r's Ex. 134). Dr. Forsthuber acknowledged that where Dr. Axelrod used the software appropriately and compared three proteins (and not just two), he, at most, found one amino acid homology and that was between human keratin 17, NALP5/MATER, and HPV6 L1. *Id.* (citing Pet'r's Exs. 135–36). Dr. Forsthuber argued that "it should be clear to anyone . . . that there is no meaningful overlap between NALP5/MATER, α-enolase, and HPV L1 proteins." *Id.* Dr. Forsthuber wrote that for Dr. Axelrod to claim that he found meaningful sequence homologies indicative of molecular mimicry is "baffl[ing]" because his searches "disprove[]" his claims. *Id.* at 18, 20. He therefore maintained that Dr. Axelrod's clustal searches and alleged sequence similarities are "meaningless" and "do not provide evidence of molecular mimicry in [Petitioner's] case or in POI in general." *Id.* at 18.

Further, Dr. Forsthuber indicated that there is no scientifically accepted method to substantiate whether a particular sequence homology would be evidence of molecular mimicry or "have any relationship to the development of a disease process in humans." *Id.* He argued that the role of molecular mimicry in autoimmune conditions has not been established based on sequence homologies but found by "the presence of autoantibodies . . . that showed [evidence of] cross-reactivity between pathogens and human proteins." *Id.* at 9–10 (citing Resp't's Ex. M4 at 6, ECF No. 172-5).[71] Fourneau et al. sought to examine the role of mimicry in autoimmune diseases and stated that while sequencing was the traditional approach, the "identity of limited sequence stretches is not an indication of cross-reactive mimicry[.]" Resp't's Ex. M4 at 4. Dr. Forsthuber maintained that "there is no evidence for [molecular mimicry] in [Petitioner's] case[.]" *See* Resp't's Ex. M at 9, 11, 13.

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of five to nine homologous amino acids is not sufficient to show molecular mimicry. *Id.* (citing Resp't's Ex. M5, ECF No. 172-6; Resp't's Ex. M8, ECF No. 172-9; Resp't's Ex. M9, ECF No. 172-10). Rather, he argued that the optimal length of a peptide for binding to major histocompatibility complex molecules is "approximately 18–20 amino acids." *Id.* at 13 (citing Resp't's Ex. M7, ECF No. 172-8). Dr. Forsthuber argued that Dr. Axelrod's alleged HPV molecular mimic of 3 amino acids is "dramatically shorter" than the optimal length. *Id.* Dr. Forsthuber also took issue with Dr. Shoenfeld's proposed 5-amino acid sequence homologies. *Id.* at 13. However, after careful consideration, I have already credited Petitioner's proposed minimum sequence length of 5 amino acids in my Ruling on *Althen* prong one. *See Brayboy,* 2021 WL 4453146, at *1.

[71] J. Fourneau et al., *The elusive case for a role of mimicry in autoimmune diseases,* 40 MOL. IMMUNOL. 1095–102 (2004).

He addressed the lack of autoimmune comorbidity in Petitioner's case. Dr. Forsthuber pointed out that Petitioner's treating physicians did not feel that she suffered from an autoimmune condition. *Id.* at 5. He noted Petitioner's 2022 psoriasis diagnosis and wrote that when Petitioner was seen by the same treating dermatologist in 2021, "no diagnosis of psoriasis was made." *Id.* Dr. Forsthuber argued that Petitioner's psoriasis was "[t]herefore . . . not evident until [twelve] years after the HPV vaccination and diagnosis of POI." *Id.* He continued that regardless of the time gap, psoriasis is "frequently found in the population and [] is not associated with POI." *Id.* at 6. He therefore opined that there is no reliable evidence of any autoimmune comorbidity in Petitioner's case. *Id.* at 5.

Dr. Forsthuber discussed the time of onset of Petitioner's POI but did not provide an onset date. Rather, based on Petitioner's medical records, Dr. Forsthuber argued that the onset of Petitioner's amenorrhea is "unclear[.]" *Id.* at 6. He wrote that Petitioner's petition indicates that her menstrual cycle stopped immediately following receipt of her HPV vaccine, while her medical records place the onset of amenorrhea in October of 2010. *Id.* He specifically noted that Petitioner's medical records contain "conflicting reports as to the onset of hot flashes and menstrual cycle problems," including both immediately post vaccination versus August or October of 2010. *Id.* at 19. As he could not make a determination, Dr. Forsthuber deferred to Dr. Welt regarding the onset of Petitioner's POI. *Id.* at 6, 19.

D. Corinne Welt, M.D.

Dr. Welt agreed that Petitioner suffers from POI but disputed that her POI is autoimmune in nature. Resp't's Ex. N at 3, 5. As support, Dr. Welt pointed out that in her original report, Petitioner's own expert Dr. Pinhas-Hamiel stated that the cause of Petitioner's POI was not autoimmune. *Id.* at 5 (citing Pet'r's Ex. 17 at 5–7; Pet'r's Ex. 27 at 6–8). Dr. Welt criticized Dr. Pinhas-Hamiel's reversal from her original contention, that no serum test can confirm that a woman has autoimmune POI, to her most recent assertion, that data shows a relationship with a positive ANA and autoimmune POI. *Id.* at 6 (citing Pet'r's Ex. 17 at 5–7). Dr. Welt noted that Petitioner's only positive antibody test results were two positive ANAs on "10/2011 and 11/2011."[72] *Id.* at 3–4. These results, Dr. Welt argued, "are not specific for POI." *Id.* at 4 (citing Resp't's Ex. N10, ECF No. 173-11).[73]

As support for her argument that a positive ANA is not specific to autoimmune POI, Dr. Welt also discussed the medical literature Dr. Pinhas-Hamiel relied on. *Id.* at 6. Dr. Welt wrote that Dr. Pinhas-Hamiel "quot[ed] the rate of positive ANA tests in four small studies of women with POI and normal karyotype, and no additional testing for common causes of POI[,] including *FMR1* premutations." *Id.* (citing Pet'r's Ex. 137 at 6–7). Dr. Welt noted that the Miyake et al. study that found positive ANAs in 40% of patients did not show that any patients had an autoimmune disease. *Id.* (citing Pet'r's Ex. 146). Dr. Welt criticized the Ishizuka et al. study because the ANA test used was "created in house[,]" and the data was compared to women with fertility issues, not a healthy control group. *Id.* (citing Pet'r's Ex. 140). Dr. Welt pointed out that none of the subjects had autoimmune diseases. She also pointed out that none of the subjects with

[72] This notation seems to be incorrect. Petitioner's positive ANA in 2011 occurred on July 27, 2011.

[73] A. Hoek et al., *Premature Ovarian Failure and Ovarian Autoimmunity,* 18:1 ENDOCR. REV. 107–34 (1997).

a positive ANA titer had positive localized antibody testing, thus "failing to support the positive ANA test[.]" *See id.* (citing Pet'r's Ex. 140). Dr. Welt attacked Dr. Pinhas-Hamiel's reliance on the Zhen et al. article because the authors demonstrated that the rate of positive ANA tests was not different in women with POI and control women. *Id.* (citing Pet'r's Ex. 142). Specifically, Zhen et al. found that the rate of positive ANAs in both groups did not reach statistical significance. *See* Pet'r's Ex. 142. Dr. Welt noted that the Cameron et al. study found that among adolescent patients with POI, 41.1% (7/17) of subjects were found to have a positive ANA. Resp't's Ex. N at 6 (citing Pet'r's Ex. 141 at 2). The authors wrote that of these subjects, 57.1% (4/7) had only "weakly positive titers of 1:160 or less." Pet'r's Ex. 141 at 2. The authors determined that the clinical significance of this rate is "unknown because estimates of ANA positivity in healthy individuals range from 5 to 30% in adults[.]" *Id.* at 4. They noted that "[o]nly three of [their] subjects had high ANA titers that may be associated with autoimmune disease." *Id.* Dr. Welt relied on the authors' notations and argued that their findings support her assertion that the rate of positive ANA in POI patients is similar to the rate of a positive ANAs in the normal population. Resp't's Ex. N at 6 (citing Pet'r's Ex. 141; Resp't's Ex. N14, ECF No. 173-15; Resp't's Ex. N17, ECF No. 173-18).[74]

Tan et al. sought to determine the range of ANAs in healthy individuals compared to patients with autoimmune diseases, including SLE, scleroderma, Sjögren's syndrome, and RA. Resp't's Ex. N14 at 1. The authors found that the frequency of a positive ANAs "did not differ significantly" between the two groups. *Id.* Based on their findings, the authors cautioned that ANA determinations "should not be used indiscriminately as a method to distinguish between normal individuals and patients in various disease groups." *Id.* at 10. Wananukul et al. undertook to compare the positive ANA rate between healthy children and children with SLE. Resp't's Ex. N17 at 1. They examined two-hundred seven healthy children and fifty-two children with SLE and found 15% and 91%, respectively, had a positive ANA. *Id.* The authors determined the positive predictive value for a positive ANA and the development of an autoimmune condition was 57%, with a negative predictive value of 97%. *Id.* Based on this finding, the authors indicated that patients with a positive ANA are at "minimal risk" to develop an autoimmune disease. *Id.* at 4. Dr. Welt therefore argued that Dr. Pinhas-Hamiel's references would not "support the assertion that a positive ANA at a titer of >1:160 would indicate an autoimmune cause of POI[]" in Petitioner. Resp't's Ex. N at 6.

Dr. Welt provided additional context for the factors for autoimmune POI that I identified in my ruling on *Althen* prong one. She explained the importance of adrenal antibodies and/or oophoritis[75] in establishing an autoimmune etiology for POI. *See id.* at 4 (citing Resp't's Ex. N3); *see also Brayboy*, 2021 WL 4453146, at *8. Dr. Welt argued that the presence (or absence) of adrenal antibodies "best discriminate autoimmune POI from POI of other etiologies." Resp't's Ex. N at 4. Dr. Welt further described the connection between autoimmune oophoritis and POI. *Id.* She explained that oophoritis presents with amenorrhea in the presence of multiple, large follicles seen in a pelvic ultrasound, in conjunction with low levels of estradiol. *Id.* (citing Resp't's Ex.

[74] E.M. Tan et al., *Range of Antinuclear Antibodies in "Healthy" Individuals,* 40:9 ARTHR. & RHEUMA. 1601–11 (1997); S. Wananukul et al., *Prevalence of Positive Antinuclear Antibodies in Healthy Children,* 23 ASIAN PAC. J. ALL. & IMMUNOL. 153–57 (2005).

[75] Oophoritis is inflammation of the ovary. *Dorland's* at 1323.

N19, ECF No. 173-20).[76] Dr. Welt wrote that "POI is the clinical end stage for women with autoimmune oophoritis." *Id.* (citing Resp't's Ex. N4, ECF No. 173-5; Resp't's Ex. N7, ECF No. 173-8).[77]

Regarding Petitioner, Dr. Welt opined that "there is no evidence of autoimmunity that would affect the ovary or the adrenal gland" indicative of autoimmune POI. *Id.* at 3. Dr. Welt maintained that while Petitioner had positive ANA tests over the years, she "remains negative for the majority of autoimmune factors tested[]" and had no evidence of "clinically documented autoimmune disease." *Id.* at 6. Dr. Welt argued that "[m]ost importantly, [P]etitioner had no evidence of autoimmunity to the adrenal gland with negative 21-hydroxylase antibodies documented in [April of 2022]." *Id.* at 4. She highlighted that Petitioner had negative adrenal antibodies at all other times when tested and presented no other evidence for adrenal insufficiency. *Id.* at 5 (citing Pet'r's Ex. 14 at 121). Dr. Welt noted that Petitioner underwent pelvic ultrasounds "with no evidence of large follicles indicative of oophoritis." *Id.* (citing Pet'r's Ex. 3 at 11–13). Dr. Welt maintained that the absence of adrenal autoimmunity precludes autoimmunity as a cause of POI in Petitioner's case. *Id.* at 8.

Dr. Welt addressed the onset of Petitioner's POI and opined that "it is difficult to determine the precise start date of her POI." *Id.* at 3. Dr. Welt argued that the difficulty in pinpointing the onset of Petitioner's POI is owed to the absence of "contemporaneous menstrual history in her medical records and her use of hormonal contraception on and off for several years[.]" *Id.* For instance, Dr. Welt indicated that the notes from Petitioner's May 25, 2010 gynecology visit stated that her last menstrual period was May 23, 2010, but she highlighted that no "additional menstrual history was found in the note." *Id.* She argued that without contemporaneous menstrual history in Petitioner's medical records, normal menstruation pre vaccination "cannot be proven." *Id.* at 4–5. Rather, "[o]n the contrary, there is some evidence that [Petitioner's] menstrual cycles were not regular[,] and evaluation has been confounded by [use of] hormonal contraception" between 2006 and 2010. *Id.* at 5.

She noted Petitioner's history of birth control use and that "importantly, [it] will prevent hot flashes and mask underlying menstrual problems." *Id.* at 3. Specifically, Dr. Welt indicated that Petitioner had been prescribed birth control "multiple times (Depot [sic] Provera 10/13/2006, Orthotricyclen [sic] 11/27/2007, [and] Orthrotricyclen [sic] after 3/20/2009)." *Id.* at 4. Dr. Welt noted that such contraceptive use could have blocked hot flashes or irregular menses during that time. *Id.* at 3 (citing Pet'r's Ex. 8 at 32). She also noted that Petitioner was prescribed birth control pills as of May 25, 2010. *Id.* Dr. Welt argued that due to Petitioner's documented use of hormonal contraceptives it is impossible to show that Petitioner had normal menstruation before her June 4, 2010 Gardasil vaccination. *Id.* at 4.

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[76] C. Welt et al., *Selective Theca Cell Dysfunction in Autoimmune Oophoritis Results in Multifollicular Development, Decreased Estradiol, and Elevated Inhibin B Levels,* 90(5) J. CLIN. ENDOCR. & METABOL. 3069–76 (2005).

[77] P. Bannatyne et al., *Autoimmune Oophoritis: A Clinicopathologic Assessment of 12 Cases,* 9 INT. J. GYNECOL. PATH. 191–207 (1990); E. Gloor et al., *Autoimmune Oophoriti,* 81:1 AM. J. CLIN. PATH. 105–09 (1984).

As additional support for her opinion that it is difficult to determine the onset of Petitioner's POI, Dr. Welt discussed Petitioner's earlier menstrual history and highlighted that Petitioner's medical records show a potential period of amenorrhea prior to that at issue in 2010. *Id.* at 3. Specifically, during a visit on April 26, 2007, Petitioner's last menstrual period was noted as "8/2006," approximately eight months earlier. *Id.* Dr. Welt hypothesized that this period of amenorrhea could be due to a Depo Provera injection that Petitioner received on October 13, 2006. *Id.* However, she wrote that such birth control "lasts [three] months and would not explain continued amenorrhea for [eight] months." *Id.*

Dr. Welt acknowledged Petitioner's two prior pregnancies during 2006 to 2009 but argued that such occurrences "would not rule out the diagnosis" of POI during that timeframe. *Id.* Dr. Welt wrote that "pregnancies do occur in women with POI." *Id.* (citing Resp't's Ex. N1, ECF No. 173-2; Resp't's Ex. N15, ECF No. 173-16).[78] Dr. Welt cited the Alper et al. study that discussed six women who were able to conceive after being diagnosed with POI. Resp't's Ex. N1 at 1. Two of the women conceived while receiving estrogen therapy; two while taking oral contraceptives; and two spontaneously. *Id.* Taylor et al. likewise found that women with POI still ovulate and can conceive. Resp't's Ex. N15 at 5.

Although Dr. Welt was unable to determine the exact onset date of Petitioner's POI, she generally discussed the time it takes for the development of autoimmune POI. Resp't's Ex. N at 4. Dr. Welt wrote that the lymphocytic infiltration and eventual ovarian destruction required for autoimmunity to be a cause of POI takes seventeen months to over two years to develop. *Id.* As support, Dr. Welt relied on a self-authored study. *Id.* (citing Resp't's Ex. N19).[79] Welt et al. described the clinical course of three women with presumptive autoimmune oophoritis who went on to develop POF. Resp't's Ex. N19 at 1. Among their findings, the authors observed that all three subjects had adrenal antibodies, antibodies to 21-hydroxylase, and P450 side chain cleavage antibodies. *Id.* at 1, 5. They documented "follow up history" for the three patients and noted that patient 1 had a positive ANA titer two years after her initial presentation and three years later experienced complete ovarian destruction, with her FSH in the postmenopausal range. *Id.* at 5. Patient 2 had FSH levels in the postmenopausal range 1.5 years after her initial presentation, and patient 3 exhibited such levels 17 months after her initial presentation. *Id.* The authors did not address the trigger of POI in these patients. *See id.*

The Taguchi et al.[80] study, also cited by Dr. Welt, used mouse models of oophoritis induced after a thymectomy to identify early signs of lymphocyte infiltration and early oophoritis. Resp't's Ex. N at 8 (citing Resp't's Ex. N13, ECF No. 173-14). Taguchi et al. found that the first signs of

[78] M. Alper et al., *Pregnancies After Premature Ovarian Failure,* 67:3 OBST. & GYNECOL. 59–63 (1986); A. Taylor et al., *A Randomized, Controlled Trial of Estradiol Replacement Therapy in Women with Hypergonadotropic Amenorrhea,* 81:10 J. CLIN. ENDOCR. & METABOL. 3615–23 (1996).

[79] C. Welt et al., *Selective Theca Cell Dysfunction in Autoimmune Oophoritis Results in Multifollicular Development, Decreased Estradiol, and Elevated Inhibin B Levels,* 90(5) J. CLIN. ENDOCR. & METABOL. 3069–76 (2005).

[80] O. Taguchi et al., *Autoimmune oophoritis in thymectomized mice: detection of circulating antibodies against oocytes,* 40 CLIN. EXP. IMMUNOL. 540–53 (1980).

oophoritis, or the appearance of autoantibodies against the ooplasma of oocytes,[81] "was first demonstrated at day 30–40 in [the] sera of [] mice, whose ovaries showed a marked enhancement of follicular degeneration and the death of numerous oocytes . . . ." Resp't's Ex. N13 at 1. The titer levels of such autoantibodies increased at day 50–90 and diminished and eventually disappeared at day 150–360 "when no oocytes remained in the atrophic ovary." *Id.*

She further relied on a study by Altuntas et al.[82] wherein the authors immunized female mice with peptides derived from mouse inhibin-α activates CD4+ T cells and were able to induce autoimmune oophoritis followed by POF. Resp't's Ex. N at 6 (citing Resp't's Ex. N2 at 2, ECF No. 173-3). The authors found that ovaries from mice taken "early" after immunization showed hypertrophic ovaries with an increased number of follicles, overall consistent with continued ovulation. Resp't's Ex. N2 at 6. The authors found that "[i]n sharp contrast," ovaries from mice taken 43 to 45 weeks post immunization "consistently appeared atrophic with few follicles[.]" *Id.* Altuntas et al. determined this latter "morphology" was consistent with POF, but the former was not. *Id.*

Dr. Welt applied the findings in these studies and argued that according to her own research, the incitement of autoreactive immune cells resulting in total destruction of the ovaries "take[s] time." Resp't's Ex. N at 7 (citing Resp't's Exs. N2, N13, N19). She further argued that the time between Petitioner's vaccination inducing autoreactive cells and POI diagnosis is "inconsistent with [Petitioner's] causal mechanism because an autoimmune process would take much longer to cause complete ovarian destruction[.]" *Id.* at 8. She argued "the destruction of the follicles in a human ovary would take more than two months after the trigger of an autoimmune process." *Id.* at 4. In Petitioner's case, however, Dr. Welt noted there were only two months between her Gardasil vaccination and manifestation of end stage POI with elevated FSH and low estradiol in August of 2010. *Id.* at 7 (citing Pet'r's Ex. 2 at 50). Dr. Welt argued that Dr. Pinhas-Hamiel's assertion that an immune-mediated response causing hormonal consequences would take only a few weeks is "very unlikely." *Id.* She therefore opined that Petitioner's June 4, 2010 HPV vaccine more likely than not did not cause Petitioner's POI. *Id.* at 8.

Additionally, Dr. Welt discounted Petitioner's psoriasis diagnosis and argued that there is no evidence of a comorbid autoimmune disease in Petitioner. *Id.* Dr. Welt wrote that while one of Petitioner's treaters "suggested" that she had psoriasis, "that is not an autoimmune disease associated with POI." *Id.* at 5 (citing Resp't's Ex. N10).[83] Hoek et al. listed autoimmune diseases associated with POI to some degree, including Addison's disease, oophoritis, gastric abnormalities such as Crohn's disease, thyroid abnormalities, Graves' disease,[84] Hashimoto's disease,

[81] An oocyte is "the immature female reproductive cell prior to fertilization, derived from an oogonium and occurring in two stages, primary and secondary oocytes." *Dorland's* at 1322.

[82] C. Altuntas et al., *Autoimmune Targeted Disruption of the Pituitary-Ovarian Axis Causes Premature Ovarian Failure,* 177 J. IMMUNOL. 1988–96 (2006).

[83] A. Hoek et al., *Premature Ovarian Failure and Ovarian Autoimmunity,* 18:1 ENDOCR. REV. 107–34 (1997).

[84] Graves' disease is "a syndrome of diffuse hyperplasia of the thyroid, with a female predominance; it usually has an autoimmune etiology and has been linked to autoimmune thyroiditis. Characteristics include hyperthyroidism . . . usually with goiter and ophthalmic symptoms[.] Most patients have circulating thyroid-

myasthenia gravis, positive ANAs, RA, SLE, and vitiligo. *See* Resp't's Ex. N10 at 12–15. This list did not include psoriasis. *See id.* Based on this list, Dr. Welt called Petitioner's experts' contention that Petitioner's POI must be autoimmune since other autoimmune disorders are associated with POI, "tenuous." Resp't's Ex. N at 5.

V. Legal Standard

The Vaccine Rules afford the special master discretion in choosing whether to hold a hearing, stating that he or she "may decide a case on the basis of written filings without an evidentiary hearing." Vaccine Rule 8(d); *see also Plummer v. Sec'y of Health & Hum. Servs.,* 24 Cl. Ct. 304, 307 (1991). Under the Vaccine Act, a petitioner may prevail in one of two ways. First, a petitioner may demonstrate that she suffered a "Table" injury—i.e., an injury listed on the Vaccine Injury Table that occurred within the time period provided in the Table. § 11(c)(1)(C)(i). "In such a case, causation is presumed." *Capizzano v. Sec'y of Health & Hum. Servs.*, 440 F.3d 1317, 1320 (Fed. Cir. 2006); *see* § 13(a)(1)(B). Second, where the alleged injury is not listed in the Vaccine Injury Table, a petitioner may demonstrate that she suffered an "off-Table" injury. § 11(c)(1)(C)(ii). Petitioner does not assert a Table claim in this case.

In attempting to establish entitlement to a Vaccine Program award of compensation for an off-Table claim, a petitioner must satisfy all three of the elements established by the Federal Circuit in *Althen*. *Althen* requires that a petitioner establish by preponderant evidence that the vaccinations she received caused her injury "by providing: (1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury." 418 F.3d at 1278.

Each of the *Althen* prongs requires a different showing. Under *Althen* prong one, petitioners must provide a "reputable medical theory," demonstrating that the vaccine received *can cause* the type of injury alleged. *Pafford v. Sec'y of Health & Hum. Servs.,* No. 01-165V, 2004 WL 1717359, at *4 (Fed. Cl. Spec. Mstr. July 16, 2004), *aff'd*, 64 Fed. Cl. 19 (2005), *aff'd*, 451 F.3d 1352 (Fed. Cir. 2006). To satisfy this prong, a petitioner's theory must be based on a "sound and reliable medical or scientific explanation." *Knudsen v. Sec'y of Health & Hum. Servs*., 35 F.3d 543, 548 (Fed. Cir. 1994). As indicated above, I have already determined that the petitioners in the consolidated POI cases have presented a persuasive medical theory pursuant to *Althen* prong one, describing the HPV vaccine's role in the development of autoimmune POI. *See* Findings of Fact at 24, ECF No. 147; *Brayboy*, 2021 WL 4453146, at *1. Therefore, in order to succeed under the remaining prongs of *Althen*, Petitioner must now show by preponderant evidence that her POI is autoimmune in nature.

The second *Althen* prong requires petitioners to demonstrate that the vaccine actually did cause the alleged injury. *Althen,* 418 F.3d at 1279; *Pafford,* 451 F.3d at 1352. This requires proof of a logical sequence of cause and effect, usually supported by facts derived from a petitioner's medical records. *Althen*, 418 F.3d at 1278; *Andreu v. Sec'y of Health & Hum. Servs.*, 569 F.3d 1367, 1375–77 (Fed. Cir. 2009). In Program cases, contemporaneous medical records and the

stimulating immunoglobulins that cause excessive secretion of thyroid hormones by binding to TSH receptors on thyroid follicular cells." *Dorland's* at 534.

opinions of treating physicians are favored. *Capizzano,* 440 F.3d at 1319–20 (citing *Althen*, 418 F.3d at 1280). This is because "treating physicians are likely to be in the best position to determine whether 'a logical sequence of cause and effect show[s] that the vaccination was the reason for the injury.'" *Id.* In addition, "[m]edical records, in general, warrant consideration as trustworthy evidence . . . [and] are generally contemporaneous to the medical events." *Cucuras v. Sec'y of Health & Hum. Servs.,* 993 F.2d 1525, 1528 (Fed. Cir. 1993). However, there is no presumption that medical records are accurate and complete as to all the patient's physical conditions. *Kirby v. Sec'y of Health & Hum. Servs.,* 997 F.3d 1378, 1383 (Fed. Cir. 2021). While a special master must consider these opinions and records, they are not "binding on the special master or court." 42 U.S.C. § 300aa-13(b)(1). Rather, when "evaluating the weight to be afforded to any such . . . [evidence], the special master . . . shall consider the entire record . . . ." *Id.*

The third *Althen* prong requires establishing a "proximate temporal relationship" between the vaccination and the injury alleged. *Althen*, 418 F.3d at 1281. This prong requires a petitioner to show that the timing of the injury fits with the causal theory. *Id.* at 1278. In other words, a petitioner must offer "preponderant proof that the onset of symptoms occurred within a timeframe which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation." *de Bazan v. Sec'y of Health & Hum. Servs*., 539 F.3d 1347, 1352 (Fed. Cir. 2008); *Shapiro v. Sec'y of Health & Hum. Servs*., 101 Fed. Cl. 532, 542 (2011), *recons. denied after remand on other grounds*, 105 Fed. Cl. 353 (2012), *aff'd without op.,* 503 F. App'x. 952 (Fed. Cir. 2013); *Koehn v. Sec'y of Health & Hum. Servs*., No. 11-355V, 2013 WL 3214877 (Fed. Cl. Spec. Mstr. May 30, 2013), *mot. for review denied* (Fed. Cl. 2013), *aff'd*, 773 F.3d 1239 (Fed. Cir. 2014). For example, if the petitioner's theory involves a process that takes several days to develop after vaccination, an injury that occurred within a day of vaccination would not be temporally consistent with that theory. Conversely, if the theory is one that anticipates a rapid development of a reaction post vaccination, the development of the alleged injury weeks or months post vaccination would not be consistent with that theory. The special master cannot infer causation from temporal proximity alone. *See Thibaudeau v. Sec'y of Health & Hum. Servs.*, 24 Cl. Ct. 400, 403–04 (1991); *see also Grant v. Sec'y of Health & Hum. Servs.*, 956 F.2d 1144, 1148 (Fed. Cir. 1992). In this case, Petitioner must show an appropriate temporal relationship consistent with her accepted biological mechanism of molecular mimicry.

VI. Analysis

A. Experts

Although special masters have the discretion to be informed by past rulings and experiences, case-specific filings and testimony are the most helpful types of evidence, given the fact-specific nature of each decision. *See Doe v. Sec'y of Health & Hum. Servs.*, 76 Fed. Cl. 328, 338–39 (2007). To that end, experts are an essential piece of a petitioner's claim and Respondent's defense. Where both sides offer expert testimony, a special master's decision may be "based on the credibility of the experts and the relative persuasiveness of their competing theories." *Broekelschen v. Sec'y of Health & Hum. Servs.*, 618 F.3d 1339, 1347 (Fed. Cir. 2010) (citing *Lampe v. Sec'y of Health & Hum. Servs.*, 219 F.3d 1357, 1361 (Fed. Cir. 2000)). This case ultimately turns, not only on Petitioner's medical history, but also the persuasiveness of the written reports and supporting documentation. I therefore must assess each expert's opinion and assign

weight accordingly. This assessment will inform my analysis pursuant to each remaining prong of *Althen*.

I cannot ignore that Dr. Welt is the only expert with any direct clinical experience diagnosing and treating patients with POF out of the four experts that presented opinion evidence in this case. More notably, Dr. Welt is among the leading clinical investigators in reproductive endocrinology and has personally treated "over 100" patients with POI. Resp't's Ex. N at 1. Through her care of such patients, she has acquired extensive knowledge and experience in determining, when possible, the underlying cause of POI in each of those patients. *See id.* Her academic research is also rooted in determining the etiology of POI and, in pursuit of that, she has authored numerous pieces of medical literature on the subject. *Id.* None of the remaining experts for either party has a comparable level of expertise in the alleged injury or field.

The only other expert with any apparent familiarity with the alleged injury is Dr. Pinhas-Hamiel. However, Dr. Pinhas-Hamiel's experience with POI is only tangentially related to the injury at issue because she admittedly only deals with providing the "[w]ork-up diagnosis for amenorrhea[.]" *See* Pet'r's Ex. 137 at 1. Dr. Pinhas-Hamiel is an endocrinologist, and her relevant subspecialties are in pediatrics and diabetes. *See, e.g.*, *id.* at 1–2. As Petitioner is an adult who does not suffer from diabetes, Dr. Pinhas-Hamiel's knowledge and experience in pediatric endocrinology does not provide direct support for her opinion regarding an autoimmune etiology for Petitioner's POF. When considering the parties' arguments in relation to the immunologic response involved in Petitioner's condition, Dr. Welt's clinical experience therefore contributed significantly more to the value of her testimony than Dr. Pinhas-Hamiel's. Similarly, Drs. Axelrod and Forsthuber primarily practice in the field of immunology. This subject-matter expertise would have been helpful support for a thorough discourse on the probability of an autoimmune etiology for Petitioner's POI, pursuant to *Althen* prong two.

Instead, both experts' reports heavily focused on *Althen* prong one, general causation analysis. As I have noted, Petitioner's biological mechanism has been litigated and established by preponderant evidence. Therefore, Drs. Axelrod's and Forsthuber's lengthy discussions were not helpful on that issue, nor for a determination of the etiology for Petitioner's POI. In my previous ruling, I explicitly warned the parties that my findings related to *Althen* prong one would not be relitigated nor expanded, absent advances in the medical research. *See Brayboy,* 2021 WL 4453146, at *11. Still, the two experts spent a great deal of time rebranding previous arguments. Neither expert relied on advances in the medical literature. Respondent's expert Dr. Forsthuber attacked the general acceptance of molecular mimicry, while Dr. Axelrod undercut the specificity and applicability of Petitioner's original mechanism. I have already made detailed and informed findings regarding the parties' arguments on *Althen* prong one. The experts' current renewed arguments regarding molecular mimicry, the accepted sequence length of homologies, and the relevant autoantibodies found in autoimmune POI, have been litigated. My original findings apply and are summarized below for context for the prong two analysis.

B. *Althen* Prong One

As noted above, I found that the POI petitioners "have articulated a sound and reliable theory of how the HPV vaccines could cause autoimmune POI via molecular mimicry." *Brayboy,*

2021 WL 4453146, at *1. Specifically, I indicated that the POI petitioners' experts described how "autoantibodies can attack multiple short peptide chains contained within proteins needed for normal ovarian function, when said peptides are also contained within viral proteins identified by the immune system for destruction." *See id.* In arriving at that conclusion, I already determined that the POI petitioners' expert successfully identified, and Respondent's experts failed to negate, specific points of potential cross-reactions between components of the vaccine and homologous proteins in the body that are directly responsible for the health and productivity of the ovary. *See id.* at *19. I specified that "[i]t is true that a penta-peptide chain is undisputedly short. However, given the multifactorial pathogenesis of POI, I f[ound] it logical that cross-reactions between multiple, short peptides within proteins relevant to oocyte function and in HPV vaccines may produce an ovary-specific autoimmune attack." *Id.*

In order to succeed under this theory and the remaining prongs of *Althen*, each POI petitioner must show it is more likely than not that she suffers from POI with an autoimmune etiology. *See id.* In cases where there is evidence of lymphocytic oophoritis, adrenal or ovarian autoantibodies, and comorbid autoimmune disorders, I will presume the POI is autoimmune in nature. *Id.* at *8–*11. If all three of these factors are not present, a petitioner may still be able to establish it more-likely-than-not that her POI is autoimmune, given her particular medical history. *Id.* If, for example, a petitioner has another autoimmune disorder associated with POI, such as Addison's disease, along with anti-ovarian antibodies, that may be sufficient. *Id.* I cautioned the POI petitioners that if a petitioner's clinical presentation is not at all consistent with a POI etiology, i.e., there is no evidence of oophoritis or anti-steroid antibodies, it is unlikely that she will be able to show how her POI could be characterized as autoimmune in nature. *Id.* I further warned that the presence of autoimmune co-morbidities without other factors will likely not be sufficient to establish an autoimmune etiology. *Id.*

If all three of these enumerated factors are not present, a petitioner may still be able to establish it more-likely-than-not that her POI is autoimmune, given her medical history. For example, a petitioner that has other more common characteristics of a systemic immune reaction, such as inflammation, prolonged fever, and fatigue, may also be able to establish that her individual diagnosis is autoimmune in nature, when considered with other POI symptoms. *See id.* at *1.

C. *Althen* Prong Two

The parties do not dispute that Petitioner suffers from POI. However, they dispute that Petitioner suffers from POI with an autoimmune etiology. The evidence in the record does not support Petitioner's contention that her POI is autoimmune by a preponderant standard. Petitioner is therefore unable to satisfy her burden under *Althen* prong two.

i. Laboratory Testing for Autoantibodies

Petitioner's laboratory testing was consistently negative for the autoantibodies that have been associated with autoimmune POI. As noted in my ruling on *Althen* prong one, current medical literature identifies adrenal autoantibodies as the most significant marker of autoimmune POI. *See Brayboy,* 2021 WL 4453146, at *8 (indicating that markers of ovarian autoimmunity include "antibodies directed against steroid-producing cells of various endocrine glands such as adrenal cortex cells and theca cells of the ovary[.]"). Petitioner's testing for adrenal autoantibodies was

consistently negative. For instance, her first post-vaccination laboratory testing for adrenal autoantibodies occurred on March 17, 2012, and was negative. Pet'r's Ex. 5 at 23–29, 33–36, 47. Laboratory test results from February 5, 2015, and April 8, 2022, were also negative for adrenal autoantibodies. *See* Pet'r's Ex. 121 at 3. While less specific to a determination of autoimmune POI, Petitioner's laboratory testing for anti-ovarian antibodies was also negative on March 17, 2012, and she was not re-tested at any point after her POI diagnosis or during treatment. *See Brayboy,* 2021 WL 4453146, at *8 ("[I]n general, '[a]ntiovarian antibodies . . . are too nonspecific to be of use in identifying which patients have an autoimmune mechanism.'"); *see also* Pet'r's Ex. 5 at 23–29, 33–36, 47. Petitioner's negative laboratory testing for relevant autoimmune antibodies fails to provide any support for an autoimmune etiology for her POI.

ii. Evidence of Adrenal Insufficiency

The lack of positive testing for the relevant autoantibodies does not by itself preclude Petitioner from establishing an autoimmune etiology for her POI. In fact, medical literature referring specifically to atypical cases, shows that patients with POI may still have an autoimmune etiology even without the presence of adrenal autoantibodies. *See Brayboy,* 2021 WL 4453146, at *9 (indicating that typically, if a patient fails to have adrenal autoantibodies, she will also fail to show signs of autoimmune oophoritis on biopsy; but highlighting that there may be atypical cases that do not fit such a conclusion). To establish an autoimmune etiology for POI without the presence of adrenal autoantibodies, Petitioner may exhibit other symptoms or clinical manifestations of adrenal insufficiency, such as evidence of oophoritis. *See id.* at *11. Autoimmune lymphocytic oophoritis can be diagnosed via pelvic ultrasound or testing for 21-hydroxylase autoantibodies. *See id.* at *8; *see also* Resp't's Ex. N at 4; Resp't's Exs. N3, N19.

Petitioner underwent two pelvic ultrasounds, on December 17, 2010, and February 7, 2011, following the onset of her POI symptoms. *See* Pet'r's Ex. 3 at 12–13. Petitioner's December 17, 2010 ultrasound revealed one follicle measuring 12 x 9 mm on her normal-sized right ovary. *Id.* at 13. Her February 7, 2011 ultrasound showed one follicle measuring 5 x 4 mm on her normal-sized right ovary. *Id.* at 11. During both of Petitioner's pelvic ultrasound examinations, the technician searched for, but was unsuccessful in visualizing, her left ovary and noted that it "was not clearly seen." *See id.* at 11, 13. The test's inability to show the left ovary precluded the finding of follicles on said ovary. However, neither exam revealed the presence of multiple, large follicles consistent with oophoritis. *See id.* Dr. Welt credibly explained that the presence of a single follicle is inconsistent with the presence of multiple, large follicles, in conjunction with low levels of estradiol, and therefore does not meet the criteria for an autoimmune oophoritis diagnosis. *See* Resp't's Ex. N at 4. Petitioner did not present preponderant evidence that her ultrasound results support a finding of autoimmune oophoritis, nor did her expert make such an argument. Similarly, Petitioner's laboratory testing for adrenal insufficiency, including for 21-hydroxylase antibodies on April 8, 2022, was negative. *See* Pet'r's Ex. 121 at 3. Therefore, Petitioner has failed to establish proof of adrenal insufficiency by a preponderance of the evidence.

iii. Anti-nuclear Antibodies (ANAs)

Petitioner's extensive and repeat laboratory testing and autoimmune workups yielded positive results for ANAs on July 27, 2011, and February 6, 2017. Pet'r's Ex. 9 at 72; Pet'r's Ex.

24 at 38. Petitioner relies on these results, in part, as evidence of molecular mimicry and to support an autoimmune etiology for her POI. Petitioner's expert testimony, however, provided the best evidence against a relationship between ANAs and autoimmune POI. Dr. Pinhas-Hamiel conceded that "[s]ome individuals . . . may have a positive test for ANA and yet never develop any autoimmune disease." Pet'r's Ex. 137 at 8. Additionally, the medical literature submitted explains that a positive result for ANAs is not specific for the development of many autoimmune diseases, including autoimmune POI. This lack of specificity is illustrated by positive ANA tests in healthy patients. Cameron et al. indicated that a positive ANA can be found in 5 to 30% of healthy individuals. Pet'r's Ex. 141 at 2, 4. Pashnina et al. likewise echoed Cameron et al.'s findings and found the same interval of positive ANAs in healthy patients. Pet'r's Ex. 143 at 9–11. The authors went so far as to note that ANAs "belong to the integral part of the normal functioning of the immune system." *Id.* at 3. Respondent's submitted literature by Bloch et al. includes an explicit warning against relying on a positive ANA in the diagnosis of autoimmune disease. Resp't's Ex. M1 at 3. The authors also provided explanations for a positive ANA that do not implicate autoimmune etiology, such as when a patient has a family history of autoimmune disease. *Id.* Such consistent findings in the medical literature shows by a preponderance of evidence that a positive ANA test does not, without more, predict autoimmune disease.

The same medical literature submitted by Petitioner shows that while a positive ANA is known to be associated with some systemic autoimmune diseases, POI is not one of them. Pashnina et al. extensively listed conditions wherein a positive ANA is known and, in some cases, used for diagnostic purposes. Pet'r's Ex. 143 at 7. Before addressing this list in more detail, I must define association and diagnostic value. An association refers to "the occurrence together of two or more characteristics more often than would be expected by chance alone."[85] Diagnostic value refers to the importance of any symptom that provides evidence for making a specific diagnosis.[86] These terms can be distinguished from each other. Pashnina et al. illustrated this point and how such principles can also overlap. The authors explained that positive ANAs may serve as one of many diagnostic tools in the case of autoimmune diseases known to be associated with positive ANAs. *See id.* Among Pashnina et al.'s list of autoimmune diseases associated with a positive ANA is scleroderma, Sjögren's syndrome, mixed connective tissue disease, RA, autoimmune hepatitis, anemia associated with autoimmune atrophic gastritis, Hashimoto's disease, ITP, and other conditions. *See id.* It is compelling that the authors took care to list approximately twenty autoimmune diseases (including some diseases which are not generally considered to be related to autoimmunity) wherein an association with positive ANAs is known and/or cited to as support for the diagnosis of such conditions, but that POI was not included. *Id.*

Petitioner's reliance on the Pashnina et al. article to explain her fluctuating positive and negative ANAs does not advance her case. *See* Pet'r's Ex. 137 at 8. Petitioner merely cited the authors' summary of findings in a growing number of un-filed studies that determined that the level of autoantibodies decreases (rather than increases) during exacerbations of some autoimmune diseases. *See* Pet'r's Ex. 143 at 3. For example, the Pashnina et al. article cited to a publishing by Churilov et al. when discussing the argument that a decrease in autoantibodies could reflect or

[85] M. Stöppler, *Medical Definition of Association,* MEDICINENET (March 29, 2021), https://www.medicinenet.com/association/definition.htm.
[86] *Diagnostic Value,* COLLINS DICTIONARY https://www.collinsdictionary.com/dictionary/english/diagnostic-value (last visited Feb. 14, 2023).

even cause a pathological process in the body. *Id.* Assuming the authors' conclusion is true, Pashnina et al. did not sufficiently elaborate on this summary, and Petitioner did not file the Churilov article for consideration. I will not speculate as to why Petitioner ultimately did not submit this article, but without it, I cannot consider it in more detail. More importantly, the authors did not discuss POI, and Petitioner did not relate the diseases mentioned in the article back to POI for analogy. Without more, I am unable to use the Pashnina et al. article to explain her fluctuating ANA levels. I am also persuaded by Respondent's position that Petitioner's positive ANA tests are irrelevant to a determination of an autoimmune etiology. As a result, Petitioner's two positive ANAs do not provide preponderant evidence for an autoimmune etiology for her POI.

iv. Autoimmune Comorbidity

In my ruling on *Althen* prong one, I identified "comorbid autoimmune" disorders such as Addison's disease, as a conjunctive factor in my determination of autoimmune etiology. *Brayboy,* 2021 WL 4453146, at *1. Petitioner argues that her psoriasis is a comorbid autoimmune disease that evinces her predisposition for autoimmune POI. Respondent's expert Dr. Welt effectively critiqued Petitioner's psoriasis diagnosis, and her argument is persuasive but not determinative. Petitioner visited her dermatologist, Dr. Garshick, in 2021, and she diagnosed Petitioner with only acne and dermatofibroma at that time. *See* Pet'r's Ex. 123 at 10–13. When Petitioner returned on August 19, 2022, Dr. Garshick referred to Petitioner's psoriasis as "established/worsening[.]" *See id.* at 6–9. Yet, a prior diagnosis of psoriasis does not appear in her record, either by Dr. Garshick or any other treater. Furthermore, a diagnosis of psoriasis does not appear in Petitioner's medical record after August 19, 2022. Dr. Welt is correct that Dr. Garshick's notation regarding Petitioner's psoriasis diagnosis is ambiguous. In Program cases however, the opinions of treating physicians are favored. *Capizzano*, 440 F.3d at 1326 (citing *Althen*, 418 F.3d at 1280). Indeed, when reviewing the record, a special master must consider the opinions of treating physicians. *Id.* After a consideration of the entire treatment record, including Petitioner's presentation and Dr. Garshick's assessment, I will defer to Dr. Garshick's opinion that Petitioner suffered from psoriasis.

I must note that while Petitioner contends that evidence supports a psoriasis diagnosis as early as 2012 or 2013, this argument is contrary to the record. In fact, while Petitioner reported to rheumatologist Dr. Reddy that she received a differential diagnosis of eczema or psoriasis in mid-2012, Dr. Reddy's treatment notes from March 28, 2013, ruled out psoriasis. Pet'r's Ex. 6 at 3. Dr. Reddy also recorded that Petitioner said her differential diagnosis in 2012 was made by an ENT. *See id.* at 1. Without contemporaneous medical records from a treating ENT who opined Petitioner suffered from psoriasis, I am unable to rely on her statement alone. Indeed, Petitioner's statement to Dr. Reddy approximately one year later does not carry the same weight as would a medical record created contemporaneously to the event in question. Instead, Petitioner's contemporaneous medical records refute a psoriasis diagnosis in 2013.

Petitioner submitted literature that generally discusses how psoriasis is thought to be an autoimmune disease. *See, e.g.*, Pet'r's Exs. 126–27. It falls short of Respondent's submitted literature that directly discusses autoimmune disorders that primarily involve adrenal or thyroid insufficiencies and are known to be associated with POI. *See* Resp't's Ex. N10 at 12–15. Of note, Hoek et al. listed Addison's disease, oophoritis, gastric abnormalities such as Crohn's disease,

thyroid abnormalities such as Graves' disease, Hashimoto's disease, myasthenia gravis, RA, SLE, and vitiligo as autoimmune diseases associated with POI. *See id.* This list did not include psoriasis. Lastly, Petitioner's psoriasis, first noted in her medical record approximately twelve years post vaccination, does not have an appropriate temporal relationship to her POI symptom onset. After careful consideration of Petitioner's psoriasis onset and diagnosis, the record fails to establish how this condition provides preponderant support for an autoimmune etiology of Petitioner's POI.

Petitioner also has a family history of autoimmunity, specifically a grandmother with scleroderma, a chronic autoimmune condition. Pet'r's Ex. 6 at 1. Consequently, Petitioner underwent testing for scleroderma, specifically for the presence of SCL-70 antibodies on February 6, 2017, with negative results. Therefore, her family history is less persuasive evidence of a predisposition for Petitioner to develop an autoimmune disease. This is especially true because all of Petitioner's clinical testing and symptomology directly contradicts signs of autoimmunity in her case. Petitioner has not shown it more likely that she had a predisposition for the development of an autoimmune disease based on autoimmune comorbidities.

v. Systemic Immune Reaction

Another avenue for the POI petitioners to support an autoimmune etiology of their POI is by showing symptoms of a systemic immune reaction in the medical record. This showing would need to include evidence of inflammation, prolonged fever, and fatigue, apart from POI symptomology. *See Brayboy,* 2021 WL 4453146, at *11. Petitioner underwent testing for signs of inflammatory factors on December 16, 2010, including ESR and rheumatoid factor, with negative results. Pet'r's Ex. 2 at 41–42. Her testing for CRP, another inflammatory marker, was likewise negative on February 6, 2017. Pet'r's Ex. 24 at 41. The results from these common clinical tests used to measure inflammation therefore provide significant evidence against autoimmunity and a systemic immune response in Petitioner. Likewise, Petitioner did not complain of, nor did her treaters document, a fever at any point during her diagnosis or treatment of POI. The only sign of a systemic immune reaction supported by Petitioner's medical record is fatigue. For instance, during Petitioner's first post vaccination visit with treaters on August 6, 2010, she complained of a "change in energy status[.]" Pet'r's Ex. 2 at 59. By March 20, 2017, her treater listed "chronic fatigue" among her diagnoses. Pet'r's Ex. 24 at 1. However, fatigue is a common, non-specific symptom. Without other signs of a systemic immune reaction, it is not sufficient to satisfy Petitioner's burden by a preponderant standard. Therefore, Petitioner has failed to provide preponderant evidence of an autoimmune etiology for her POI.

vi. Opinions Regarding Autoimmunity

The record fails to support Petitioner's treater Dr. Gleicher's opinion on autoimmunity, relied upon by Petitioner. Although the opinions of treating physicians are to be favored in the Program, I must consider such notations in light of the entire record. *Capizzano,* 440 F.3d at 1319–20 (citing *Althen*, 418 F.3d at 1280) ("In Program cases, contemporaneous medical records and the opinions of treating physicians are favored."); *see also* 42 U.S.C. § 300aa-13(b)(1) ("While a special master must consider these opinions and records, they are not "binding on the special master or court." Rather, when "evaluating the weight to be afforded to any such . . . [evidence], the special master . . . shall consider the entire record . . . ."). While Dr. Gleicher wrote on March 17, 2012, that he thought Petitioner's POI was "likely autoimmune," his notation is negated by the

rest of the record. *See* Pet'r's Ex. 5 at 7. Indeed, he ordered and ran a battery of tests on Petitioner for autoimmune serologies, including autoantibodies and other inflammatory markers, and the results were all negative. *See id.* at 23–29, 33–36, 47. After such testing, Dr. Gleicher did not further note his opinion that Petitioner suffered from autoimmune POI. *See generally id.* at 1–55. As a result, I will not credit Dr. Gleicher's March 17, 2012 notation as preponderant evidence of autoimmunity.

I must also note that some of the evidence submitted by Petitioner in this case is contradictory. Petitioner's expert, Dr. Pinhas-Hamiel, authored a report early on during the pendency of Petitioner's case, and then a supplemental report following my ruling on *Althen* prong one. Her first report took the position that Petitioner's POI was not autoimmune, because she did not have signs of autoimmune disorders, such as hypo or hyperthyroidism, and she did not have antibodies to the "thyroid gland, to the ovaries or to adrenals." Pet'r's Ex. 17 at 5. However, following my ruling regarding the factors necessary for establishing an autoimmune etiology, Dr. Pinhas-Hamiel reversed her opinion in her supplemental report, authored approximately seven years later, and argued that support for Petitioner's autoimmune POI was found in her positive ANAs. Pet'r's Ex. 137 at 7–8. Petitioner's argument is undermined by the reversal with no explanation or acknowledgment of her expert's prior position. Petitioner cannot have it both ways simply to meet new criteria.

Overall, Petitioner has failed to present preponderant evidence that she suffers from lymphocytic oophoritis, has relevant autoantibodies, has a comorbid autoimmune disorder associated with POI, or that her clinical presentation was at all consistent with autoimmune POI. In light of the cumulative evidence discussed, pursuant to the factors enumerated in my ruling on prong one, Petitioner is unable to show it more likely than not that she suffers from POI with an autoimmune etiology.

D. *Althen* Prong Three

Petitioner has failed to meet her burden under *Althen* prong three. As previously discussed, early during the pendency of this case, the presiding special master held a hearing to determine the first symptom or manifestation of POI to assess whether this case was barred by the statute of limitations. *See Culligan,* 2016 WL 3101981, at *10. Indeed, the presiding special master determined that in women over 18 years of age, the development of menstrual irregularities that exceed "normal" variation, such as secondary amenorrhea and cycle and frequency irregularities, are the first symptoms or manifestation of POI, irrespective of the petitioner's date of diagnosis. *See id.* at *7–*9. While the presiding special master found that Petitioner's case was not time barred, such findings are now applicable to my *Althen* prong three analysis.

Only two of the four experts in this case explicitly opined regarding the date of onset of Petitioner's POI. While Dr. Welt applied the definition outlined in *Culligan*, that menstrual irregularities such as amenorrhea are the first manifestations of POI, the record does not provide preponderant support for Dr. Welt's arguments on onset. Dr. Welt argued that the onset of Petitioner's POI occurred sometime prior to her June 4, 2010 HPV vaccination, and as early as 2006. Resp't's Ex. N at 3. As support, she cited Petitioner's use of hormonal contraceptives off and on from 2006 to 2010 and argued that she could have been having symptoms of POI during

that period, but such manifestations were blocked by the use of birth control.[87] *See id.* Dr. Welt's argument is not supported by Petitioner's medical history pursuant to a preponderant standard. Indeed, Petitioner's records show she was prescribed hormonal contraceptives approximately once per year, on October 13, 2006, November 27, 2007, March 20, 2009, and May 25, 2010. *See* Pet'r's Ex. 8 at 20, 32, 41, 46, 48; Pet'r's Ex. 2 at 61. However, Petitioner's medical records do not establish that she was consistently using such medications as prescribed. In fact, Petitioner's 2006 and 2008 pregnancies are strong evidence that she was likely not using such contraceptives consistently. Pet'r's Ex. 8 at 8, 38, 41. Therefore, Dr. Welt's argument that birth control use blocked symptoms of Petitioner's POI is speculative at best and does not provide preponderant evidence that Petitioner's POI began pre vaccination.

Dr. Welt reinforced her argument that the onset of Petitioner's POI occurred between 2006 and 2007, based on medical records that note a potential period of amenorrhea prior to vaccination. Resp't's Ex. N at 3. She relied on Petitioner's April 26, 2007 negative pregnancy test document, that listed her last menstrual period as August of 2006, as proof of amenorrhea for eight months from August of 2006 to April of 2007. *See id.* However, Dr. Welt could not say with certainty that Petitioner experienced amenorrhea during this time, opining that she "may have had" it prior to August of 2010. Petitioner's medical records did not otherwise mention or discuss menstrual irregularities or periods of amenorrhea during 2006 and 2007. In fact, Dr. Welt pointed out that Petitioner's medical records were notably and consistently lacking information regarding the dates of her last menstrual cycles, around that time and beyond. Without contemporaneous medical records or sufficient support from the record, Dr. Welt's ambiguous and unsupported argument cannot be afforded much weight. Instead, Dr. Welt admitted that it is "difficult" to pinpoint the onset of Petitioner's amenorrhea and POI symptoms and did not otherwise provide a specific onset date aside from saying it began pre vaccination. *See id.* Dr. Welt's arguments therefore do not provide preponderant evidence for the onset of Petitioner's POI.

Indeed, as Dr. Welt correctly highlighted, Petitioner's medical records are unclear regarding symptoms of menstrual irregularities, such as secondary amenorrhea and cycle infrequencies. This is due, in part, to the lack of pre-vaccination menstrual history generally contained in Petitioner's medical records. It is also due to Petitioner's failure to report and describe signs of amenorrhea as they allegedly occurred. For example, Petitioner presented to her gynecologist on August 6, 2010, and did not report any lack of menstruation or changes to her cycle. *See* Pet'r's Ex. 2 at 59. She reported other gynecologically-related issues, as will be discussed in more detail below, but she did not mention menstrual infrequencies or amenorrhea at that time. *See id.* However, on December 7, 2010, approximately four months later, Petitioner told a different treater that by August of 2010, she had missed her cycle "for about [three] months[,]" or since roughly May of 2010, which prompted her gynecologist to take her off birth control and monitor her hormone levels. Pet'r's Ex. 3 at 32. This is consistent with visit notes from Petitioner's gynecologist on May 25, 2010, that noted the date of Petitioner's last cycle on May 23, 2010. Pet'r's Ex. 2 at 66. I will not speculate as to why Petitioner did not report menstrual irregularities or cycle infrequencies to her gynecologist on August 6, 2010. *See, e.g.*, *LaLonde v. Sec'y of Health & Hum. Servs.,* 110 Fed. Cl. 184, 203–04 (2013), *aff'd*, 746 F.3d 1334 (Fed. Cir. 2014) (outlining

[87] I must note that while *Culligan* provided findings regarding how contraceptive use will impact conclusions regarding the onset of POI, such findings were applicable to statute of limitations issues, not *Althen* prong three. *Culligan,* 2016 WL 3101981, at *10.

four potential explanations for inconsistencies between contemporaneously created medical records and later testimony or accounts: "(1) a person's failure to recount to the medical professional everything that happened during the relevant time period; (2) the medical professional's failure to document everything reported to her or him; (3) a person's faulty recollection of the events when presenting testimony; or (4) a person's purposeful recounting of symptoms that did not exist."); *see also Matthews v. Sec'y of Health & Hum. Servs.,* No. 19-414V, 2021 WL 4190265, at *5 (Fed. Cl. Spec. Mstr. Aug. 19, 2021) (internal citations omitted) (acknowledging that "the absence of a reference to a condition or circumstance [in contemporaneous medical records] is much less significant than a reference which negates the existence of the condition or circumstance."). Despite Petitioner's August 6, 2010 record, I find her medical record from December 7, 2010, wherein she documented her history and described missing her cycle for three months prior to August of 2010, provides preponderant support for her menstrual irregularities and amenorrhea beginning in May of 2010.

It is true that Petitioner's subsequent medical records do not mention or discuss periods of amenorrhea, but they also do not consistently contain the date of her last menstrual cycle. They likewise do not reflect if the absence of a notation regarding the date of Petitioner's last menstrual cycle is indicative of an irregularity or if such information simply was not sought. When the submitted records do reference the date of Petitioner's last menstrual cycle, they seem to reflect that Petitioner did experience menstrual cycles during 2010. I do not have before me evidence to determine the precise regularity of her cycles, but there is some evidence in Petitioner's medical record that she did not experience her cycle every month after May of 2010. For example, while Petitioner did note during her August 6, 2010 gynecology visit that she experienced a cycle on August 1, 2010, her record does not indicate if she experienced cycles in the preceding months of June or July. Therefore, this record does not contradict Petitioner's account of irregular menstruation or amenorrhea beginning in May of 2010. *See* Pet'r's Ex. 12 at 3. There is no indication in the record whether Petitioner's cycle resumed in September of 2010. Subsequent records show she had menstrual cycles in October and November of 2010. Pet'r's Ex. 3 at 10–12. In December of 2010, she reported that her cycle was "again" two weeks late, but she did not otherwise indicate when her last menstruation occurred. *Id.* at 32–33. Petitioner's medical records from 2011 provide a bit more clarity and add context to Petitioner's 2010 records. On February 7, 2011, Petitioner reported that her last cycle occurred in November of 2010. *Id.* at 10. This is consistent with Petitioner's report on December 7, 2010, that her cycle was approximately two weeks late. *Id.* at 32–33. While it is not certain when Petitioner's amenorrhea began, certainty is not the standard in the Program. There is preponderant evidence that Petitioner experienced menstrual irregularities and amenorrhea beginning in May of 2010. Consistent with *Culligan*, the onset of Petitioner's POI was therefore more likely than not in May of 2010.

The first symptom of Petitioner's POI therefore began pre vaccination. As I have determined that Petitioner has not presented preponderant evidence that her condition began following her June 4, 2010 vaccination, and she has failed to establish an autoimmune etiology for her POI, it is impossible for me apply her biological mechanism and analyze her claim under *Althen* prong three. Indeed, Petitioner's claim must fail under prong three because if a condition began before vaccination, it would be logically impossible to infer that Petitioner's injury occurred "within a timeframe for which . . . it is medically acceptable to infer causation-in-fact." *See W.C.*

v. Sec'y of Health & Hum. Servs., 704 F.3d 1352, 1360 (2013). Although my analysis could end there, for the sake of completeness, I will address the parties' remaining arguments.

The record does not provide preponderant evidence for Dr. Axelrod's arguments on onset. Despite *Culligan's* finding that the first symptom or manifestation of POI is menstrual irregularities, including secondary amenorrhea, Dr. Axelrod argued that Petitioner's manifestation of POI occurred when she started experiencing hot flashes, "sometime" around or before July 23, 2010. *See* Pet'r's Ex. 124 at 9–10. As support for this approximation, he relied on Petitioner's report during her August 6, 2010 visit, with gynecologist Dr. Selitsky, that she had been having hot flashes "for the last two weeks." Pet'r's Ex. 2 at 59. As previously noted, while *Culligan* defined amenorrhea as the first symptom of POI, both *Culligan* and *Brayboy* account for and describe other clinical symptoms of POI, such as hot flashes. *Culligan,* 2016 WL 3101981, at *7; *Brayboy,* 2021 WL 4453146, at *7–*9. Thus, even if I accepted Dr. Axelrod's argument that Petitioner's hot flashes were the first manifestation of her POI, her claim still fails under *Althen* prong three because the onset of this symptom was far outside what is consistent with her biological mechanism.

In arriving at this conclusion, I must first address the onset of Petitioner's hot flashes. Her medical records show that she began experiencing hot flashes as early as the end of July of 2010, and by no later than the beginning of August of 2010. *See* Pet'r's Ex. 2 at 59 (reporting hot flashes for the last two weeks on August 6, 2010); *But see* Pet'r's Ex. 3 at 32 (reporting hot flashes beginning in August of 2010). While there is a slight distinction in these timeframes (end of July vs. beginning of August), I do not consider it to be consequential. The record establishes it more likely than not that Petitioner was experiencing hot flashes by approximately August 1, 2010.

Assuming *arguendo* that Petitioner's hot flashes on or around August 1, 2010, signaled the onset of her POI, the two-month timeframe between her June 4, 2010 vaccination and August 1, 2010 onset, is inconsistent with her biological mechanism. Indeed, this timeframe for the progression of Petitioner's injury is beyond what is accepted for an immune-mediated response to trigger Petitioner's mechanism of molecular mimicry. In fact, Petitioner's submitted medical literature by Abbas et al. shows that an immune-mediated response following exposure to an antigen can be expected to take two weeks. Pet'r's Ex. 130. Likewise, Petitioner's submitted literature by Lawley et al. shows that an immune response occurs within ten to twenty-five days. Pet'r's Ex. 131. A period of approximately two months is far greater than the ten to twenty-five day or two-week interval for an immune-mediated response to occur following exposure to an antigen as reported by Lawley et al. and Abbas et al.

Notably, however, Petitioner's submitted literature does not discuss POI generally, autoimmune POI, or POI triggered by the HPV vaccine. It merely provides a general overview of immune-mediated responses and/or addresses the development of serum sickness. Serum sickness is an acute or subacute hypersensitivity reaction. *See, e.g.*, *supra,* note 46 (defining serum sickness as "a hypersensitivity reaction to the administration of foreign serum or serum proteins . . . caused by the formation of circulating antigen-antibody complexes that are deposited in tissues and trigger tissue injury mediated by complement and polymorphonuclear leukocytes."). The acute or subacute onset of serum sickness is consistent with the mechanism of an immune-mediated response triggering molecular mimicry. *See, e.g.*, Pet'r's Ex. 131. An acute or subacute process

via molecular mimicry is commonly seen and accepted in Program cases alleging Guillain-Barré syndrome, transverse myelitis, and other vaccine-related demyelinating injuries petitioners successfully establish occurred via molecular mimicry. *See, e.g.*, *Tracy v. Sec'y of Health & Hum. Servs.,* No. 16-213V, 2022 WL 1125281, at *34 (Fed. Cl. Spec. Mstr. Mar. 30, 2022) (finding that the onset of transverse myelitis thirteen days following receipt of a Prevnar 13 vaccine was appropriate based on the petitioner's mechanism of molecular mimicry). The acute or subacute nature of these diseases explains why a ten to twenty-five day or two-week onset following exposure to an antigen is appropriate. However, Petitioner failed to present any evidence to explain how the onset of serum sickness, an acute condition, is applicable to the onset of POI, a chronic condition, via her accepted biological mechanism of molecular mimicry. Consistent with prior successful Program cases alleging acute injuries via molecular mimicry, it stands to reason that if Petitioner had suffered an immune-mediated reaction triggering molecular mimicry in response to her June 4, 2010 HPV vaccination, she would have experienced a manifestation of her POI before August 1, 2010. Petitioner likewise did not provide persuasive evidence to explain how this two-month gap in onset is still consistent with her biological mechanism. Therefore, even applying Dr. Axelrod's arguments on onset, Petitioner's claim must still fail under *Althen* prong three.

VII. Conclusion

Petitioner has failed to establish by preponderant evidence that the HPV vaccine she received on June 4, 2010, was the cause-in-fact of her POI, as she cannot establish her POI is autoimmune and the onset is not consistent with her biological mechanism. While I am sympathetic towards Petitioner's condition and acknowledge that she has suffered both physically and emotionally, the evidence in the record does not show entitlement to compensation by a preponderant standard. Accordingly, this case is hereby **DISMISSED.**[88]

IT IS SO ORDERED.

s/Herbrina D. Sanders
Herbrina D. Sanders
Special Master

[88] Pursuant to Vaccine Rule 11(a), entry of judgment is expedited by the parties' joint filing of a notice renouncing the right to seek review.